Acta Neurochirurgica Supplement 128

Mikhail F. Chernov
Motohiro Hayashi
Clark C. Chen
Ian E. McCutcheon *Editors*

Gamma Knife Neurosurgery in the Management of Intracranial Disorders II

Springer

Acta Neurochirurgica Supplement 128

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Editors

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Editors
Mikhail F. Chernov
Faculty of Advanced Techno-Surgery
and Department of Neurosurgery
Tokyo Women's Medical University
Tokyo
Japan

Motohiro Hayashi
Faculty of Advanced Techno-Surgery
and Department of Neurosurgery
Tokyo Women's Medical University
Tokyo
Japan

Clark C. Chen
Department of Neurosurgery
University of Minnesota Medical School
Minneapolis, MN
USA

Ian E. McCutcheon
Department of Neurosurgery
The University of Texas MD Anderson Cancer Center
Houston, TX
USA

ISSN 0065-1419 ISSN 2197-8395 (electronic)
Acta Neurochirurgica Supplement 128
ISBN 978-3-030-69216-2 ISBN 978-3-030-69217-9 (eBook)
https://doi.org/10.1007/978-3-030-69217-9

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Sponsors of the Seventh Meeting of the Asian Gamma Knife Academy (October 31–November 1, 2016; Honolulu, HI, USA) and Publication of Its Proceedings

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To the inventors, providers, and practitioners of radiosurgery worldwide, who are giving real hope to so many patients.

M. F. Chernov

To all colleagues working in the field of radiosurgery; and in memory of Professor Kintomo Takakura, MD—an outstanding neurosurgeon, exceptional leader, great mentor, and phenomenal person—who pioneered the Gamma Knife in Japan and Asia, and devoted his lifelong efforts to developing this neurosurgical technique worldwide.

M. Hayashi

To a better world, where tears are not shed because of cancer.

C. C. Chen

To my teachers at the Montreal Neurological Institute and the National Institutes of Health—Drs. Gilles Bertrand, André Olivier, and Edward Oldfield—who exemplified caring, thoughtfulness, integrity, and creativity in caring for patients.

I. E. McCutcheon

Preface

The Asian Gamma Knife Training Program (AGKTP) was established in 2007 as the first and, at that time, the only international professional organization in southeast Asia that was specifically dedicated to intracranial radiosurgery. Its main goals included facilitation of the exchange of ideas and skills among practitioners in the field, continuing education of young neurosurgeons and their training in Gamma Knife surgery (GKS), and dissemination of knowledge about advances in contemporary Gamma Knife techniques to the medical communities in Asian countries. The first AGKTP Meeting was held in the same year at the Saitama Gamma Knife Center at the Sanai Hospital (Saitama, Japan), with subsequent events organized in Tokyo, Japan (in 2008); Busan, Korea (in 2009); Taipei, Taiwan (in 2010); St. Petersburg, Russia (in 2011); and Shanghai, China (in 2014). The unique features of these meetings, which made them somewhat different from typical professional conferences, comprised in-depth, up-to-date, and practice-oriented coverage of all main topics in modern GKS by educational lectures (instead of the usual scientific reports) followed by wide and open critical discussions, and hands-on workshops with demonstration of real-time radiosurgical treatment planning. To better reflect its educational and scientific objectives, the AGKTP was renamed as the Asian Gamma Knife Academy (AGKA) in 2009, although its activities have extended beyond the borders of Asia.

On October 31–November 1, 2016, the seventh AGKA Meeting was conducted at the Hawaii Advanced Imaging Institute (Honolulu, HI, USA) under the leadership of Dr. Stephen Holmes. Reflecting the specific geographical location of the venue, this event was attended mainly by experts from the USA and Japan. The highly advanced level of presentations and general success of this conference led to the decision to report its program in these proceedings under the title *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*, following the tradition of a similar volume published after the fifth AGKA Meeting held in St. Petersburg in 2011 (*Acta Neurochirurgica Supplement Volume 116*). After the preparation, collection, and thorough editing of all submitted manuscripts, herein you can see the results of our work.

The articles included in this book are dedicated to the management of benign tumors (with a special emphasis on the optimal combination of microneurosurgery and radiosurgery for attaining the best functional results in patients with vestibular schwannomas, craniopharyngiomas, and pituitary adenomas), intracranial malignancies (e.g., pituitary carcinoma and brain metastases from solid cancers), symptomatic cavernous malformations, medically refractory tremors, and intractable pain syndromes, as well as to the specific aspects of radiosurgical treatment planning and dosimetry, medical physics, neuroimaging, anesthetic support, and the history of psychosurgery. We hope that readers will find the materials presented herein scientifically interesting and practically useful, and that our work will contribute to further progress in radiosurgery worldwide for the greatest benefit of all patients.

Mikhail F. Chernov — Tokyo, Japan
Motohiro Hayashi — Tokyo, Japan
Clark C. Chen — Minneapolis, MN, USA
Ian E. McCutcheon — Houston, TX, USA

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Subtotal Resection Followed by Adjuvant Radiosurgery for Large Vestibular Schwannomas: Outcomes with Regard to the Timing and Regimen of Irradiation

Hesham Radwan, Tarek Elserry, Mark B. Eisenberg, Jonathan P. S. Knisely, Maged M. Ghaly, and Michael Schulder

Abstract *Objective:* To evaluate the results of combined management of large vestibular schwannomas (VS) with initial subtotal resection (STR) followed by adjuvant stereotactic radiosurgery (SRS), with a particular emphasis on the timing and regimen of irradiation.

Methods: Seventeen patients underwent STR of a VS followed by SRS, whereas five others were observed after STR. Early SRS (<6 months after surgery) and late SRS (>6 months after surgery) were done in 8 and 9 patients, respectively. Single- and multisession SRS treatments were administered in 10 and 7 patients, respectively. The mean follow-up durations after surgery and SRS were 40 and 28 months, respectively.

Results: The rates of radiological and oncological tumor control after SRS were 82% and 100%, respectively. The tumor volume at the last follow-up and its relative changes after SRS did not differ significantly on the basis of the irradiation timing (early versus late) or on the basis of the irradiation regimen (single-session versus multisession). In no patient who was observed after STR of a VS was tumor regrowth noted during a mean follow-up period of 49 months. At 12 months after surgery, motor function of the ipsilateral facial nerve corresponded to House–Brackmann grades I, II, III, and IV in 16 patients (73%), 3 patients (14%), 1 patient (5%), and 2 patients (9%), respectively. Facial nerve function at the last follow-up did not differ significantly on the basis of the irradiation timing (early versus late) or on the basis of the irradiation regimen (single-session versus multisession).

Conclusion: The combination of initial STR followed by adjuvant SRS is an effective treatment strategy for patients with a large VS. Although the optimal timing and regimen of postoperative irradiation of the residual lesion should be defined further, our preliminary data suggest that either early or late SRS after surgery may provide good tumor control and optimal functional results.

Keywords Combined treatment · Facial nerve function Gamma Knife radiosurgery · Linear accelerator · Multisession radiosurgery · Stereotactic radiosurgery · Subtotal removal Surgery · Vestibular schwannoma

H. Radwan
Department of Neurosurgery, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

Department of Neurosurgery, Ain Shams University, Cairo, Egypt

T. Elserry
Department of Neurosurgery, Ain Shams University, Cairo, Egypt

M. B. Eisenberg
Department of Neurosurgery, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

J. P. S. Knisely
Department of Radiation Oncology, Weill Cornell Medicine, New York, NY, USA

M. M. Ghaly
Department of Radiation Medicine, Zucker School of Medicine at Hofstra/Northwell, Lake Success, NY, USA

M. Schulder (✉)
Department of Neurosurgery, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

Brain Tumor Center, Northwell Neurosciences Insitute, Lake Success, NY, USA
e-mail: mschulder@northwell.edu

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*, Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_1,

Introduction

Vestibular schwannomas (VS) are encountered with an incidence of 1 per 100,000 person-years and comprise 75–90% of all cerebellopontine angle tumors [1, 2]. Management options include observation, microsurgical resection, stereotactic radiosurgery (SRS), and fractionated stereotactic radiotherapy (SRT). In particular, over the last 30 years, SRS has become a standard treatment option for patients with small or medium-sized VS, and there is strong evidence that it not only provides effective tumor control but also allows more favorable results of facial nerve function preservation than microsurgical resection of the lesion. For example, in a prospective study performed by Pollock et al. [3], normal facial movements at follow-up were noted significantly more often in patients treated with SRS than in those who underwent surgery (100% versus 61% at 3 months, $P < 0.001$; 100% versus 69% at 12 months, $P < 0.001$; and 96% versus 75% at the last follow-up visit, $P < 0.01$). However, SRS in patients with a large VS results in lower tumor control rates (of around 82–88%) and is associated with a higher risk of complications (mainly, cranial neuropathy) and a more frequent need for subsequent additional treatment [4–7]. On the other hand, surgery in patients with a large VS is rather challenging as well and often results in suboptimal functional outcomes [1, 8, 9]. Considering these limitations, our group has, during the last decade, adopted a novel combined treatment approach in cases of a large VS, comprising initial subtotal resection (STR) of the tumor, followed by SRS of its remnants. Our initial results with application of such a technique have been reported previously [10]. Herein, we present an additional analysis of the same clinical series directed at evaluation of tumor control and facial nerve function with regard to the timing and regimen of adjuvant irradiation, and discuss provisional advantages of clinical application of such a treatment strategy in cases of a large VS.

Patients and Methods

Demographic details of our study cohort have been presented before [10]. Briefly, our series comprised 7 men and 15 women (mean age 56 years) who were diagnosed with a large VS (maximum diameter >4 cm) corresponding to Koos stage III or IV [11, 12]. All patients underwent STR of the tumor, which in 17 cases (77%) was followed by adjuvant SRS; five other patients (23%) declined postoperative irradiation and preferred to be observed pending any evidence of tumor regrowth.

Stereotactic Radiosurgery

The mean interval between STR of a VS and SRS of the residual tumor was 9.5 months (median 7 months, range 2–50 months). Eight patients were treated within 6 months after surgery (early SRS), and 9 were treated later on (late SRS). Overall, 9 patients underwent single-session Gamma Knife surgery (GKS) with a marginal dose of 12–14 Gy delivered at the 50% prescription isodose line. Seven other patients who had either a prolonged (>3-month) postoperative recovery from cranial neuropathy or a large residual tumor (volume >3 cc) received multisession SRS with a linear accelerator (LINAC); in 6 of them, the total dose at the 80% prescription isodose line was 25 Gy, being delivered in five fractions (5 Gy per fraction), and in one, it was 21 Gy in three fractions (7 Gy per fraction). One additional patient underwent single-session LINAC-based SRS with a marginal dose of 12 Gy.

Follow-Up, Tumor Volumetry, and Outcome Measures

The mean lengths of follow-up after surgery and SRS were 40 months (median 20 months, range 20–128 months) and 28 months (median 22 months, range 17–77 months), respectively. The lesion volumes both before and after treatment were calculated with the use of iPlan® Net (Brainlab AG; Munich, Germany), and decreases or increases of ≥1 cc during follow-up were considered tumor shrinkage and tumor enlargement, respectively. Facial nerve function was assessed according to the House–Brackmann grading system [13]. In addition, trigeminal nerve function, lower cranial nerve function, vestibular function, and hearing were evaluated.

Statistics

The Mann–Whitney test and Spearman correlation were used for data analysis. P values <0.05 were considered statistically significant.

Results

The mean VS volumes before surgery, at the time of SRS after STR, and at the last follow-up after SRS were 13.1, 2.9, and 2.8 cc, respectively. The mean extent of resection (EOR) was 77%. The tumor volume at the time of SRS did not differ

significantly on the basis of the irradiation timing (early versus late: mean 4.0 versus 2.0 cc, $P > 0.05$) or on the basis of the irradiation regimen (single-session versus multisession: mean 3.4 versus 2.2 cc, $P > 0.1$). In patients who declined SRS and were observed after STR, the mean postoperative tumor volume was 0.35 cc.

Tumor Control and Volumetric Response to Radiosurgery

Tumor shrinkage, stabilization, and enlargement after SRS were noted in 1 case (6%), 13 cases (76%), and 3 cases (18%), respectively. No patient required additional treatment during follow-up. Thus, the radiological and oncological tumor control rates after SRS were 82% and 100%, respectively.

The mean lengths of follow-up in the groups of patients who underwent early and late SRS were 24 and 42 months, respectively. The tumor volume at the last follow-up did not differ significantly on the basis of the irradiation timing (early versus late: mean 3.6 versus 2.0 cc, $P > 0.1$) or on the basis of the irradiation regimen (single-session versus multisession: mean 3.3 versus 2.0 cc, $P > 0.1$). The relative changes in the tumor volume after SRS varied from −83% to +193% (mean +9%, median 0%), did not demonstrate any correlation with the preradiosurgery tumor volume ($R_s = -0.224$, $P = 0.3681$) or the time interval between STR and SRS ($R_s = 0.330$, $P = 0.1868$), and did not differ significantly on the basis of the irradiation timing (early versus late: mean −3% versus +20%, $P > 0.1$) or on the basis of the irradiation regimen (single-session versus multisession: mean +10% versus +7%, $P > 0.1$).

The mean length of follow-up in the group of patients who were observed after STR of a VS was 49 months, and in none of them was tumor regrowth noted.

Preservation of Facial Nerve Function

Anatomical preservation of the facial nerve during surgery was attained in all patients. Immediately after STR of a VS, excellent-to-moderate (House–Brackmann grades I–III) motor function of the ipsilateral facial nerve was noted in 15 of 22 patients (68%), whereas in 5 others (23%), disfiguring facial weakness was obvious (House–Brackmann grades IV–V), and 2 patients (9%) had complete facial paralysis (House–Brackmann grade VI). The postoperative House–Brackmann grade inversely correlated with the volume of the residual VS after STR ($R_s = -0.63$, $P = 0.0039$), and the best outcome was generally attained in cases with a residual tumor volume >3 cc [10].

Nevertheless, at 12-month follow-up after surgery, excellent motor function (House–Brackmann grade I), good motor function (House–Brackmann grade II), and moderate motor function (House–Brackmann grade III) of the ipsilateral facial nerve were noted in 16 patients (73%), 3 patients (14%), and 1 patient (5%), respectively, whereas in 2 others (9%), it corresponded to House–Brackmann grade IV. It was found that in patients with motor function of the ipsilateral facial nerve that corresponded to House–Brackmann grades III–V immediately after surgery, the probabilities of recovery to an excellent-to-good level (House–Brackmann grades I–II) within 6 and 18 months were >50% and approximately 80%, respectively [10].

All 8 patients (100%) who underwent early adjuvant SRS after STR had excellent (House–Brackmann grade I) motor function of the ipsilateral facial nerve at the last follow-up, in comparison with 5 of 9 patients (56%) in the late SRS group. However, statistical analysis showed that the House–Brackmann grade at the time of the last follow-up did not differ significantly on the basis of the irradiation timing (early versus late: $P > 0.1$) or on the basis of the irradiation regimen (single-session versus multisession: $P > 0.1$).

Other Outcome Measures

Temporary trigeminal neuropathy and dysphagia/dysarthria after surgery were noted in 4 patients (18%) and 2 patients (9%), respectively. Out of 7 patients who demonstrated vestibular dysfunction preoperatively, slight symptomatic improvement during follow-up after STR of the tumor was marked in 3, whereas in 4 others, pre-existing symptoms remained stable.

Temporary trigeminal neuropathy after SRS was noted in 1 patient (6%). Out of 8 patients with serviceable hearing before SRS, only one demonstrated a decline (from Gardner–Robertson class II to class IV) after irradiation. No patient showed deterioration of vestibular function after SRS.

Discussion

From the dawn of neurological surgery as a medical specialty, and for nearly a century thereafter, surgical tumor removal was the only treatment option available for patients with a VS. Novel technologies and technical developments introduced over the decades resulted in significant improve-

ments in surgical results and declines in morbidity and mortality [14]. Nevertheless, even today, gross total resection (GTR) of a VS is a highly challenging goal, and postoperative complications in such cases are not uncommon [1, 8, 9]. This is particularly true in patients with large tumors, in whom the prevalence of excellent-to-good (House–Brackmann grades I–II) facial nerve function after surgery averages only 54%, although it has ranged widely from 44% to 94% [4]. Schwartz et al. [8] reported that better facial nerve function preservation and a lower incidence of complete facial paralysis (House–Brackmann grade VI) may be achieved after near-total resection (NTR) (78% and 2%, respectively) or STR (71% and 10%, respectively) of a large VS in comparison with GTR (53% and 24%, respectively). Although the impact of the EOR on postoperative facial nerve function remains debatable, it is evident that conservative (i.e., less aggressive) surgery is associated with reduced intraoperative mechanical stress on adjacent anatomical structures, including cranial nerves. In concordance, in our series, the House–Brackmann grade immediately after STR of a VS inversely correlated with the volume of the residual lesion [10]. The problem is that incomplete surgical removal is accompanied by high rates of tumor regrowth, which were 22%, 21%, and 3% after STR, NTR, and GTR, respectively [8]. The optimal solution in such cases may be a combined treatment strategy, as was advocated in several previous reports [6, 10, 15–21] and has been presented herein.

Initial STR is directed at reduction of the VS volume and decompression of the brainstem, cerebellum, and cranial nerves, and it limits the risk of their anatomical injury so as to decrease the chance of permanent postoperative neurological deficits. The main question is when to stop resection. It should be emphasized that we are not advocating leaving large tumor remnants. Nevertheless, since the primary objective of conservative surgery in such cases is preservation of neurological function, a larger residual lesion volume (if it is small enough to allow postoperative SRS) may be considered an appropriate price for optimal functional outcome. In particular, anatomical preservation of the facial nerve is of paramount importance, but it is hardly possible to predict when it may be injured during tumor removal [22, 23]. In our experience, some patients developed postoperative facial palsy despite the absence of significant changes during intraoperative electrical stimulation of the nerve. On the other hand, the results indicate that better facial nerve function after surgery may be observed in cases with a residual tumor volume >3 cc [10]. Thus, we recommend that the volume of a residual VS should be in the range of 3 cc if this can be achieved safely.

Subsequent adjuvant SRS of a residual tumor prevents its regrowth in the same way as occurs with a smaller VS. The questions are when to perform postoperative irradiation and whether it should be done for the management of a residual lesion or at the time of its progression. This issue clearly remains controversial. It is well recognized that a residual VS may be stable after surgery for a more or less prolonged period of time. None of the patients we observed after STR demonstrated tumor regrowth during a mean follow-up duration of 49 months, while other researchers have reported that progression of an incompletely resected VS usually occurs 2–3 years after the intervention [1, 8, 22, 24, 25]. Although in the present series, early SRS was associated with the most prominent volumetric tumor response and better facial nerve function at the last follow-up, the statistical analysis did not reveal significant differences in comparison with delayed irradiation, which, however, was still done for a residual (i.e., nonprogressing) VS. Similarly, we did not find any advantages of multisession SRS, which was arbitrarily selected for patients with prolonged postoperative recovery from cranial neuropathy or in cases of a relatively large residual lesion. It should be underlined, however, that our study was retrospective and based on a limited number of cases, and the short length of follow-up did not allow differentiation between true progression of a VS and pseudoprogression, which is typically observed between 6 and 18 months after SRS. Therefore, the optimal timing and regimen of adjuvant SRS after STR of a VS should be evaluated further. A randomized, controlled trial could clarify these important issues but would be very difficult to complete, whereas use of registry-based data seems more achievable and could provide equally robust information.

In our opinion, the challenge of GTR for a large VS is an idea whose time has passed, given the benign nature of these slow-growing tumors, the high risks of facial nerve palsy and other cranial neuropathies after aggressive surgery, and the established role of SRS as a safe and effective treatment option. Several reports in the literature [6, 15–21], as well as our own results [10], indicate that in such cases, STR followed by adjuvant SRS may be quite effective and provides local tumor control rates similar to those observed after GTR, but with much more favorable functional outcomes. An important issue is that such a clinical strategy, and thus conservative surgery, should be preplanned, since it provides a 95–100% rate of preservation of facial nerve function (and even hearing in some cases) in comparison with a 35–40% rate when the decision to perform combined treatment is done intraoperatively because of an inability to attain GTR of the tumor [5, 20].

Conclusion

Patients with a large VS may be treated effectively with a combination of initial preplanned STR of the tumor followed by adjuvant SRS of its remnants. In such cases, the goal of conservative surgery is reduction of the mass lesion volume

and decompression of adjacent anatomical structures without an excessive risk of injuring them, in order to prevent a permanent postoperative neurological deficit. The optimal timing (early versus late) and regimen (single-session versus multisession) of postoperative SRS should be defined in further studies involving large numbers of patients, but our preliminary data suggest that either option may result in good tumor control and an optimal outcome—in particular, providing high rates of ipsilateral facial nerve function preservation.

Conflict of Interest The authors have no conflict of interest concerning the reported materials or methods.

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Preplanned Partial Surgical Removal Followed by Low-Dose Gamma Knife Radiosurgery for Large Vestibular Schwannomas

Yoshiyasu Iwai, Kenichi Ishibashi, and Kazuhiro Yamanaka

Abstract *Objective:* The present study evaluated outcomes after preplanned partial surgical removal of a large vestibular schwannoma (VS) followed by low-dose Gamma Knife surgery (GKS).

Methods: Between January 2000 and May 2015, 47 patients with a unilateral VS (median maximum diameter 32 mm) underwent preplanned partial tumor removal at our clinic. GKS for a residual lesion was done within a median time interval of 3 months. The median prescription dose was 12 Gy. The median length of subsequent follow-up was 74 months.

Results: The actuarial tumor growth control rates without a need for additional management at 3, 5, and 15 years after GKS were 92%, 86%, and 86%, respectively. At the time of the last follow-up, the function of the ipsilateral facial nerve corresponded to House–Brackmann grade I in 92% of patients. Significant improvement of ipsilateral hearing was noted in two patients after partial tumor removal and in one after GKS. Among 16 patients who presented with ipsilateral serviceable hearing, it was preserved immediately after surgery in 81% of cases and at the time of the last follow-up in 44%. Salvage surgical treatment was required in 9% of patients.

Conclusion: Preplanned partial surgical removal followed by low-dose GKS provides a high level of functional preservation in patients with a large VS.

Keywords Combined treatment · Facial nerve function Gamma Knife radiosurgery · Hearing preservation · Partial removal · Retrosigmoid approach · Surgery · Vestibular schwannoma

Introduction

Gamma Knife surgery (GKS) has become a mainstream treatment option for patients with a small-to-medium-sized vestibular schwannoma (VS) because it offers minimal invasiveness, optimal tumor growth control, and beneficial long-term functional results—in particular, with regard to preservation of facial nerve function and hearing [1–3]. Nevertheless, in cases of large tumors, surgical resection is clearly indicated to relieve increased intracranial pressure and cerebellar dysfunction [4, 5]. A meticulous microsurgical technique and advanced intraoperative neurophysiological monitoring allow good facial nerve preservation rates, but maintenance of serviceable hearing after tumor removal is still a significant challenge [6]. Since 1994, we have performed preplanned partial surgical tumor removal followed by GKS to improve functional outcomes in patients with a large VS [4]. Steady gains in our clinical experience have allowed this management strategy to be upgraded and optimized, and have clearly demonstrated its benefits and efficacy [7]. The objective of the present study was evaluation of the results of such combined treatment in a recent cohort of patients.

Patients and Methods

Between January 2000 and May 2015, 47 patients with a large unilateral VS (maximum diameter ≥25 mm) underwent preplanned partial tumor removal followed by low-dose GKS at our clinic (Table 1). This cohort comprised 22

Y. Iwai (✉)
Department of Neurosurgery, Tominaga Hospital, Osaka, Japan
e-mail: y-iwai@rc5.so-net.ne.jp

K. Ishibashi · K. Yamanaka
Department of Neurosurgery, Osaka City General Hospital, Osaka, Japan

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*, Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_2,

Table 1 Clinical characteristics at presentation in 47 patients who underwent preplanned partial surgical removal of a large unilateral vestibular schwannoma followed by low-dose Gamma Knife radiosurgery

Clinical characteristic	Values
Sex (*N*)	
Male	22 (47%)
Female	25 (53%)
Age (years)	
Range	30–82
Median	60
Symptoms and signs (*N*)	
Hearing impairment	43 (91%)
Cerebellar ataxia	37 (79%)
Trigeminal neuropathy	36 (77%)
Facial weakness	14 (30%)
Headache caused by increased intracranial pressure	6 (13%)
Hydrocephalus	2 (4%)
Pure tone average (*N*)	
0–30 dB	8 (17%)
31–50 dB	8 (17%)
51–80 dB	14 (30%)
81–110 dB	5 (10%)
>110 dB	12 (26%)
Maximum tumor diameter (*N*)	
25–29 mm	11 (23%)
30–39 mm	27 (57%)
40–49 mm	4 (9%)
50–52 mm	5 (11%)

men and 25 women aged from 30 to 82 years (median age 60 years). The most common preoperative symptoms and signs were hearing impairment (in 43 patients; 91%), cerebellar ataxia (in 37 patients; 79%), and trigeminal neuropathy (in 36 patients; 77%), including 1 patient with trigeminal neuralgia. Ipsilateral facial weakness was noted in 14 cases (30%) and corresponded to House–Brackmann grades II and III [8] in 12 and 2 patients, respectively. Before surgery, 16 patients (34%) had ipsilateral serviceable hearing (pure tone average (PTA) ≤50 dB), 19 (40%) showed some preservation of ipsilateral hearing (PTA >50 to ≤110 dB), and 12 (26%) were considered deaf (PTA >110 dB). The median maximum diameter of the tumor was 32 mm (range 25–52 mm). Eleven patients with smaller tumors (maximum diameter 25–29 mm) underwent initial surgical resection instead of primary GKS because of the presence of cerebellar ataxia and/or trigeminal neuropathy.

Surgical Technique

Our surgical technique for partial removal of a large VS and reduction of its size to make the mass suitable for GKS was described in detail previously [4]. In brief, the retrosigmoid approach was used in all cases, and the portion of the mass adjacent to the cerebellum was resected as much as possible, but the ventral and intracanalicular parts of the tumor were intentionally left in situ. Opening of the internal auditory canal (IAC) was avoided. Spinal or ventricular drainages were never used either intra- or postoperatively.

Radiosurgical Technique

The median interval between partial removal of a VS and GKS was 3 months (range 1–12 months). In cases of cystic tumors, GKS was done earlier (usually at 1 month after surgery) to prevent re-expansion of the cyst. The median preradiosurgery lesion volume was 2.7 cc (range 0.4–10.4 cc). Treatment planning and radiation dosimetry were done with Leksell GammaPlan® (Elekta AB; Stockholm, Sweden). The median prescription dose was 12 Gy (range 10–12 Gy). Of note, a prescription dose of 10 Gy was applied only once, for irradiation of the largest tumor in the present series, which had a volume of 10.4 cc.

Follow-Up

All patients underwent clinical evaluations, PTA measurements, and magnetic resonance imaging (MRI) examinations every 6 months during the first 3 years after GKS and, in cases of tumor growth control, yearly thereafter. The median length of follow-up after irradiation was 74 months (range 24–180 months).

Results

The rates of actuarial tumor growth control without a need for additional management at 3, 5, 10, and 15 years after GKS were 92%, 86%, 86%, and 86%, respectively (Fig. 1). Treatment failure was significantly associated with the lesion volume before irradiation (37.5% versus 3% in VS with preradiosurgery volumes of ≥6 cc versus <6 cc, $P = 0.01$) and showed a statistically nonsignificant trend toward a higher incidence in younger patients (33% versus 6% in patients aged <50 years versus ≥50 years, $P = 0.076$). The sex of the

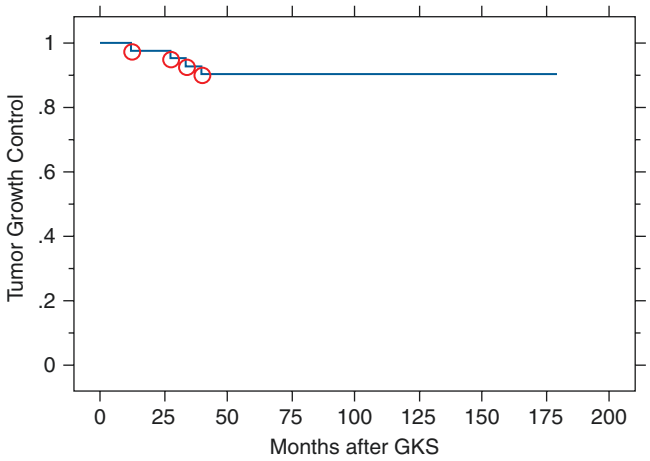

Fig. 1 Kaplan–Meier curve demonstrating tumor growth control without a need for additional management in 47 patients with a large unilateral vestibular schwannoma after preplanned partial surgical removal followed by low-dose Gamma Knife surgery (GKS)

Table 2 Preservation of motor function of the ipsilateral facial nerve in 47 patients who underwent preplanned partial surgical removal of a large unilateral vestibular schwannoma followed by low-dose Gamma Knife radiosurgery (GKS)

	Preservation of motor function (*N*)		
House–Brackmann grade	Before surgery	After surgery	At last follow-up after GKS
I	33 (70%)	37 (79%)	43 (92%)
II	12 (26%)	7 (15%)	1 (2%)
III	2 (4%)	0	0
IV	0	1 (2%)	2 (4%)
V	0	2 (4%)	1 (2%)

patient and the presence of a tumor cyst were not associated with growth control of a VS after low-dose GKS.

Preservation of Facial Nerve Function

Two weeks after partial surgical tumor removal, the motor function of the ipsilateral facial nerve corresponded to House–Brackmann grade I in 37 patients (79%) and to grade II in 7 (15%), but in 1 patient (2%), it deteriorated to grade IV and in 2 (4%), it deteriorated to grade V (Table 2). At the time of the last follow-up after GKS, the motor function of the ipsilateral facial nerve corresponded to House–Brackmann grade I in 43 patients (92%), to grade II in 1 (2%), to grade IV in 2 (4%), and to grade V in 1 (2%); in the latter patient, no substantial functional improvement was noted during the entire follow-up period after partial surgical tumor removal.

Preservation of Hearing

After partial tumor removal, two patients (6%) experienced a significant improvement in their ipsilateral hearing, with changes in PTA from 115 dB to 59 dB in one case and from 115 dB to 12.5 dB in another (Fig. 2). In addition, in one patient, a significant improvement in ipsilateral hearing with a change in PTA from 115 dB to 35 dB was noted 1.5 years after GKS.

Overall, out of 16 patients with ipsilateral serviceable hearing (PTA ≤50 dB) at presentation, 13 (81%) showed its preservation after partial tumor removal and 7 of them maintained the same level of serviceable hearing at the time of the last follow-up after GKS. Out of 35 patients with any degree of ipsilateral hearing preservation (PTA ≤110 dB) at presentation, 25 (71%) showed the same level of hearing after partial tumor removal (PTA changes within 20 dB but not exceeding 110 dB) and 11 of them maintained the same level of hearing at the time of the last follow-up after GKS.

Salvage Surgery

Following preplanned partial surgical removal and subsequent GKS, 4 patients (9%) suffered from cerebellar or truncal ataxia, which necessitated salvage surgery performed within a median interval of 31 months (range 12–42 months) after irradiation. In this group, the median VS volume before GKS was 6.6 cc (range 3.5–10.4 cc). In all cases, salvage surgery was directed at partial tumor removal with the purpose of functional preservation. During subsequent follow-up (median 84 months, range 60–96 months), two VS demonstrated gradual shrinkage; one was stable, and in the other case, enlargement of the tumor cyst necessitated stereotactic aspiration of its content via the transcerebellar approach 54 months after salvage surgery.

Complications

There were no deaths in the present series. Four patients experienced complications after partial removal of a large VS: a lung abscess due to aspiration pneumonia, aseptic meningitis necessitating steroid therapy, a pulmonary embolism, and venous infarction of the cerebellum requiring surgery directed at external decompression of the posterior cranial fossa were each noted once. In none of these cases did the development of a complication affect the overall treatment strategy.

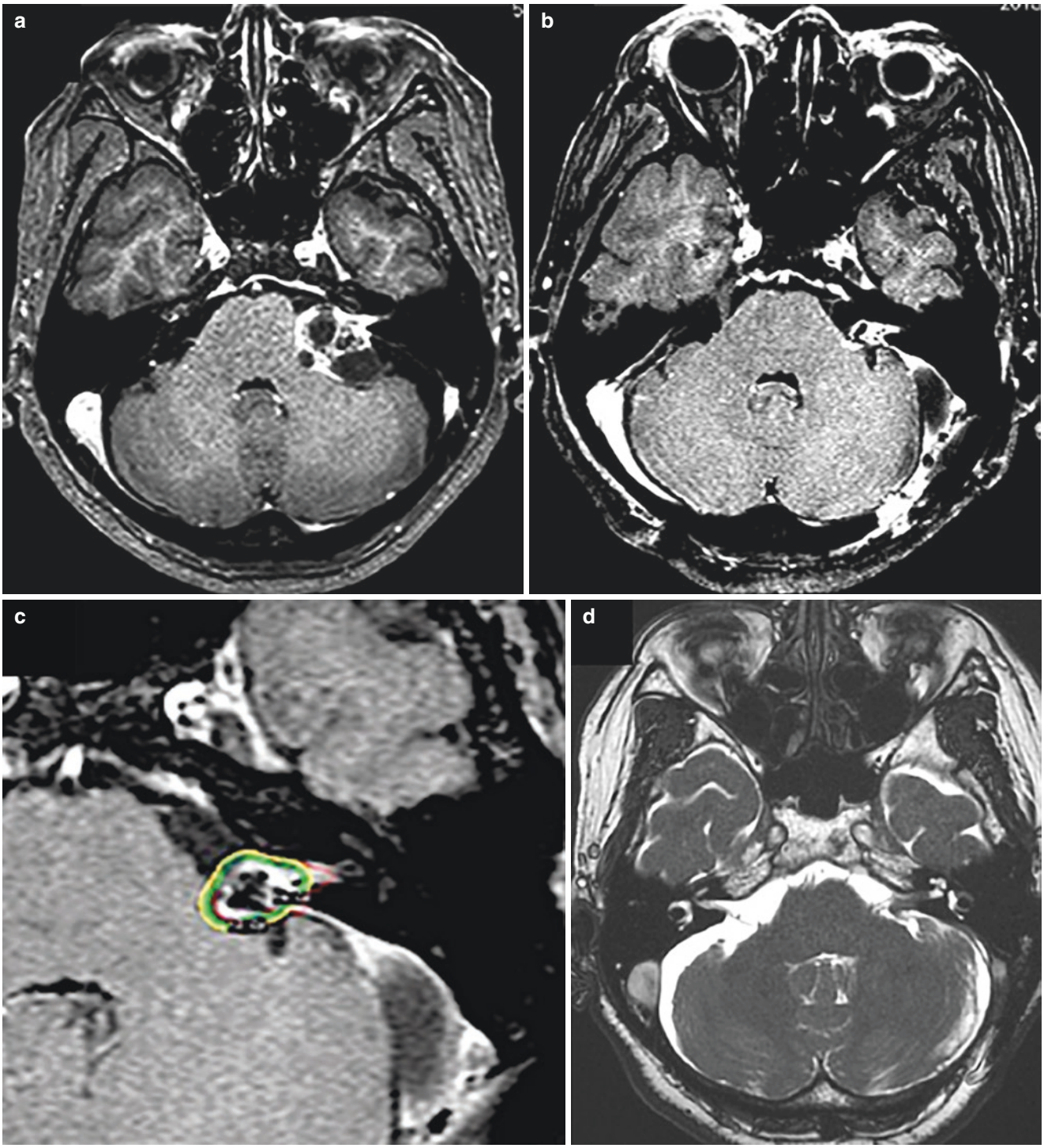

Fig. 2 Clinical example of a beneficial functional outcome after combined treatment of a 75-year-old woman with a large vestibular schwannoma, who presented with trigeminal neuropathy, cerebellar ataxia, and severe ipsilateral hearing impairment (pure tone average (PTA) 115 dB). Axial postcontrast T1-weighted magnetic resonance imaging (MRI) (**a**) demonstrated a cystic tumor within the left cerebellopontine angle, corresponding to Koos stage IV (maximum diameter 25 mm). Partial surgical removal of the lesion via the retrosigmoid approach (**b**) resulted in a significant improvement in hearing (PTA 12.5 dB; speech discrimination score 95%). Gamma Knife radiosurgery for a residual neoplasm was done 1 month later (**c**) with a prescription dose of 12 Gy (cochlear dose 3.4 Gy). At 3 years after irradiation, T2-weighted MRI showed a reduction of the lesion volume (**d**); at that time, serviceable hearing on the left side was preserved (PTA 28.5 dB)

There were no major adverse radiation effects (ARE) or permanent complications after GKS. Nevertheless, two patients had a transient hemifacial spasm (within 12–30 months after irradiation in one and within 12–48 months in the other) and two other patients had transient trigeminal neuropathy (within 6–12 months after irradiation in one and within 26–28 months in the other) associated with transient tumor enlargement.

Discussion

Nowadays, instead of undergoing microsurgical resection of their tumor, many patients with a small-to-medium-sized VS are being treated either with observation or with minimally invasive stereotactic radiosurgery (SRS) [9]. The latter option provides optimal oncological and functional outcomes [10, 11]. In particular, use of GKS in such cases results in a 97% rate of long-term tumor growth control and a 77% rate of hearing preservation, accompanied by a very low incidence of facial neuropathy (<1%) [3]. Nevertheless, because of the high risks of ARE and neurological deterioration—in particular, caused by transient tumor enlargement after irradiation—it is traditionally considered that single-session SRS is not indicated for large VS (≥3 cm in diameter) and that such tumors should undergo microsurgical resection [4, 12].

The problem is that surgery for large VS is associated with a nonnegligible risk of morbidity—in particular, related to cranial nerve function. Functional preservation of the ipsilateral facial nerve after total removal of such tumors still remains challenging and, even in the best hands, can be attained in just 42–57% of cases [13–16]; correspondingly, the reported rates of good postoperative facial nerve function (House–Brackmann grades I or II) are limited to 25–57% [13–19]. Preservation of serviceable hearing after total removal of a large VS is even more difficult, and its rates vary from 5% to 56% [6, 15, 17–23]. Preservation of cranial nerve function may be facilitated by less aggressive surgery, but in turn it may result in regrowth of the residual tumor, which is encountered in 44–53% of patients after partial removal of a VS [24, 25].

To obtain both an optimal functional outcome and appropriate long-term tumor growth control, a combined treatment strategy for a large VS with subtotal or partial surgical removal followed by GKS was suggested and has demonstrated beneficial results in several series [26–30], which corresponds well to our own experience [4, 7]. Indeed, reduction of the lesion volume facilitates subsequent irradiation with delivery of the optimal prescription dose for the residual tumor, which in turn prevents its regrowth and may provide long-term control at rates similar to those seen after GKS of a small-to-medium-sized VS.

Partial Surgical Removal of a Vestibular Schwannoma Before Radiosurgery

Generally, there are two approaches with regard to limited surgical removal of a large VS before subsequent SRS. At first, the decision on the optimal degree of tumor resection may be made intraoperatively—in particular, on the basis of the results of neurophysiological monitoring [26, 28, 30]. For example, in the series described by Yang et al. [30], incomplete tumor resection was not intentionally preplanned but was dictated by an intraoperative decision to preserve cranial nerve and/or brainstem function; thereafter, GKS was applied for residual or regrowing lesions. On the other hand, incomplete removal of a VS with the purpose of functional preservation may be planned in advance of craniotomy [4, 7, 27, 29], although it may also have some variations. For instance, Fuentes et al. [26] opened the IAC and kept in situ the portion of the tumor along the facial nerve but did not try to preserve the cochlear nerve; in contrast, in our patients [4, 7], partial lesion removal was attained without opening the IAC—an approach similar to that used in the series reported by van de Langenberg et al. [29].

Timing of Radiosurgery After Partial Surgical Removal of a Vestibular Schwannoma

In our series, GKS was usually done at 3 months after preplanned partial surgical removal of a VS, since by that time the postoperative changes have regressed and the shape of the lesion has become well suited to radiosurgical targeting [4, 7]. Moreover, in cases of cystic tumors, we prefer to perform GKS even earlier (at 1 month) to prevent re-expansion of the cyst. There may be some concerns that such a relatively short time interval between surgery and SRS may be associated with potential radiation-induced injury of the cranial nerves, which might have already been damaged to some degree during intraoperative manipulations. However, according to our experience, such a risk should not be overestimated, since no patient in the present series demonstrated symptoms or signs of ARE, permanent cranial neuropathy, or acute clinical deterioration after GKS.

Outcome After Combined Treatment

The reported rates of tumor growth control after combined treatment of a large VS with subtotal or partial surgical removal followed by GKS have varied from 79% to 100% in

series with a median follow-up duration of 30–66 months [4, 7, 26, 27, 29, 30]. As was demonstrated in the present study, as well as in others [29], approximately 8–10% of patients need salvage surgical resection of the lesion. According to our data, a preradiosurgery volume ≥6 cc is significantly associated with worse tumor growth control; therefore, at present, we try to reduce the size of the mass beyond this cutoff level during surgical removal.

According to several reports, combined treatment with incomplete surgical removal followed by GKS provides preservation of the motor function of the ipsilateral facial nerve in 86–94% of cases [26, 28–30], which is better than the preservation rate seen after total surgical removal of a large VS. In concordance with these data, good facial nerve function (House–Brackmann grade I or II) was noted in 94% of patients at the time of the last follow-up in the present series. There was no case of permanent facial palsy after irradiation, and this reconfirms the safety and efficacy of low-dose GKS (prescription dose of 11–12 Gy at the 50% isodose line).

The rates of ipsilateral serviceable hearing maintenance after incomplete removal of VS followed by SRS have varied widely in different series and strongly depend on the initial surgical strategy [27, 29]. In the series described by Pan et al. [27], the preservation rate was 100% after intracapsular decompression of the tumor but 0% after more aggressive surgery. In our patients with serviceable hearing at presentation, it was preserved in 81% of cases immediately after partial tumor removal but in only 44% at the time of the last follow-up. This corroborates the known fact of gradual deterioration of hearing after irradiation; the reported rates of ipsilateral serviceable hearing preservation after GKS of VS are 43–48% at 5 years, 34–38% at 7–8 years, and 23% at 10 years of follow-up [31, 32].

Salvage Surgery After Radiosurgery for Vestibular Schwannomas

Salvage surgical treatment after failed SRS is considered challenging for functional preservation, since irradiation may result in development of tight adhesions between the tumor capsule and adjacent anatomical structures, including cranial nerves [33]. Therefore, less aggressive resection is frequently advocated in such cases, which corresponds to our own experience [34]. In the present series, salvage surgery after GKS was performed in 9% of patients. It was intentionally directed at partial removal of the lesion, and the appropriateness of such a strategy was confirmed by the absence of tumor regrowth in any case, with a median subsequent follow-up duration of 84 months.

Of note, decision-making on salvage surgery after SRS for schwannomas should always consider the possibility of transient volumetric enlargement of the tumor, which is usually observed at 6–12 months after irradiation and is typically accompanied by loss of central lesion contrast enhancement on T1-weighted MRI [12, 35–38]. In such cases, especially in asymptomatic or minimally symptomatic patients, a policy of observation with or without steroid therapy is preferable, since subsequent shrinkage of the mass accompanied by regression of neurological symptoms may be expected in approximately 90% of cases.

Conclusion

Preplanned partial surgical removal followed by low-dose GKS may be beneficial in patients with a large VS, since it provides a high level of functional preservation, especially with regard to motor function of the ipsilateral facial nerve and hearing. Occasionally, it even results in improvement of severely impaired hearing. Surgery should preferably be directed at reduction of the mass volume to <6 cc, which is associated with significantly better tumor growth control without a need for additional management after subsequent irradiation. Further clinical experience with such a combined strategy may result in its widespread acceptance as the treatment of choice for patients with a large VS presenting with well-preserved cranial nerve function and hearing.

Conflict of Interest The authors have no conflict of interest concerning the reported materials or methods.

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Outcome After Resection of Craniopharyngiomas and the Important Role of Stereotactic Radiosurgery in Their Management

Tomokatsu Hori, Kosaku Amano, Takakazu Kawamata, Motohiro Hayashi, Genichiro Ohhashi, Shinichiro Miyazaki, Masami Ono, and Nobuhiro Miki

Abstract *Objective:* Experience with management of craniopharyngiomas (CPH) was evaluated retrospectively.

Methods: Between 1981 and 2012, 100 patients underwent removal of a CPH (the main surgical group), and an original tumor grading system was applied to these cases. The mean length of follow-up was 121 months. Additionally, 17 patients underwent removal of a CPH between 2012 and 2017 (the supplementary surgical group), and in 6 of them, CyberKnife radiosurgery was performed on a residual tumor (in 5 cases) or at the time of recurrence (in 1 case).

Results: In the main surgical group, the gross total resection (GTR) rate was 81%. The early and late disease-specific postoperative mortality rates were 0% and 2%, respectively. Tumor recurrence was never noted after GTR. There was a statistically significant increase in the Karnofsky Performance Scale (KPS) score after surgery. The tumor surgical grade was inversely associated with both the pre- and postoperative KPS scores, and was lower in cases operated on via the transnasal transsphenoidal approach, but was unrelated to the GTR rate. In the supplementary surgical group, the GTR rate was 65%. CyberKnife radiosurgery consistently resulted in tumor shrinkage.

Conclusion: GTR is the preferred management option for CPH. The original surgical grading system developed at Tokyo Women's Medical University may be helpful for clinical decision-making. CyberKnife radiosurgery for residual and recurrent CPH is associated with high tumor response rates.

Keywords Craniopharyngioma · CyberKnife radiosurgery Gamma Knife radiosurgery · Management · Multisession radiosurgery · Outcome · Resection · Stereotactic radiosurgery · Surgery · Surgical approach · Surgical classification Surgical grading · Tumor response

Introduction

A craniopharyngioma (CPH) is one of the most challenging targets for any neurosurgeon, and attainment of gross total resection (GTR) in such cases, even by experienced hands, is rather difficult [1–11]. Correspondingly, recurrence of these tumors is quite common and may manifest years after the primary surgery. Stereotactic radiosurgery (SRS) has demonstrated efficacy in management of a small residual or recurrent CPH, and is more advantageous than conventional fractionated radiotherapy (FRT) with regard to both tumor control and treatment-related complications—in particular, in pediatric patients. In cases of sellar tumors, SRS is usually delivered either using the Leksell Gamma Knife (Elekta AB; Stockholm, Sweden), with multiple cobalt 60 (^{60}Co) radiation sources, or using a modified linear accelerator (LINAC) CyberKnife (Accuray; Sunnyvale, CA, USA), which, in particular, facilitates multisession treatment [12]. However, it remains unknown whether some of these modalities provide better outcomes [12–14]. Herein, we report our experience with management of CPH, analyze the results of their resection with regard to the original surgical grading system, and evaluate

T. Hori (✉)
Moriyama Neurological Center Hospital, Tokyo, Japan

Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan
e-mail: thori@moriyamaikai.or.jp

K. Amano · T. Kawamata
Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

M. Hayashi
Faculty of Advanced Techno-Surgery and Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

Saitama Gamma Knife Center, Sanai Hospital, Saitama, Japan

G. Ohhashi · S. Miyazaki
Department of Neurosurgery, Shin-Yurigaoka General Hospital, Kawasaki, Kanagawa, Japan

M. Ono · N. Miki
Department of Endocrinology, Tokyo Neurological Center Hospital, Tokyo, Japan

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*,
Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_3,

the role of SRS with the CyberKnife in attaining tumor shrinkage during long-term follow-up in comparison with Gamma Knife surgery (GKS).

Patients and Methods

The results of surgery and SRS with the CyberKnife in patients with a CPH treated by the senior author (TH) were analyzed retrospectively.

Main Surgical Group

Detailed characteristics of our main surgical group have been highlighted previously [6]. Briefly, between 1981 and 2012, 100 patients with a CPH underwent tumor removal either by the senior author himself or under his direct supervision. This series comprised 55 males and 45 females (mean age 33.1 years, range 1–75 years) and included 36 children <15 years of age (23 boys and 13 girls; mean age 8.1 years). There were 86 newly diagnosed CPH and 14 recurrent tumors that had previously been operated on elsewhere. Before the surgery, 15 patients underwent GKS at other institutions.

Surgical Grading System for Craniopharyngiomas

Our original surgical grading system for CPH is based on scoring of tumor-associated parameters relevant for resection [6, 15]. It was developed for reliable comparison of outcomes with use of different surgical approaches, and may provide a neurosurgeon with helpful support during decision-making as to selection of the optimal treatment strategy in each individual case. On the basis of findings during preoperative plain and postcontrast magnetic resonance imaging (MRI), the following characteristics of the lesion are assessed (Table 1): the maximum sagittal diameter, the maximum coronal diameter (perpendicular to the midline), the structure, and extension with regard to the clinoidal line, the foramen of Monro, and mammillary bodies. The total score may vary from 2 to 12, which corresponds to five CPH grades: grade I (a score of 2), grade II (a score of 3–5), grade III (a score of 6–8), grade IV (a score of 9–11), and grade V (a score of 12) [6, 15].

Surgical Approach

Basically, for resection of a CPH, we preferred midline surgical access utilizing either the transnasal transsphenoidal approach (TTA) (in 25 cases) or the anterior interhemispheric (AIH) trans–lamina terminalis approach (in 61 cases) [5]. However, if the lesion extended far laterally beyond the lateral limit of the internal carotid artery (ICA), the pterional approach (PA) was applied (in 12 cases). Our surgical technique with use of these approaches in the present series was not substantially different from those described by other colleagues, with the exception of the specific suturing method used for closure of the dural opening upon completion of tumor resection via the TTA, as was originally described by the senior author in 1986 (Fig. 1). Surgery was mainly performed with use of an operative microscope, but in some cases, additional endoscope-assisted removal of the hidden part of the tumor extending beyond the ventral portion of the optic chiasm, upward or laterally, was done as well. In

Table 1 Tokyo Women's Medical University surgical grading system for craniopharyngiomas, based on scoring of tumor-associated parameters that are relevant for resection. (Adapted from Hori [15])

	Score			
Tumor-associated factor	0	1	2	3
Maximum sagittal diameter	–	<2 cm	2–4 cm	>4 cm
Maximum coronal diameter	–	<2 cm	2–4 cm	>4 cm
Structure	Cystic (single cyst)	Cystic (multiple cysts)	Mixed	Solid
Extension relative to the clinoidal line	Located above the clinoidal line	Extending below the clinoidal line	–	–
Extension relative to the foramen of Monro	Not reaching the foramen of Monro	Reaching the foramen of Monro	–	–
Extension relative to mammillary bodies	Not reaching mammillary bodies	Reaching mammillary bodies	–	–

The total score may vary from 2 to 12 and corresponds to grade I (score 2), grade II (score 3–5), grade III (score 6–8), grade IV (score 9–11), or grade V (score 12)

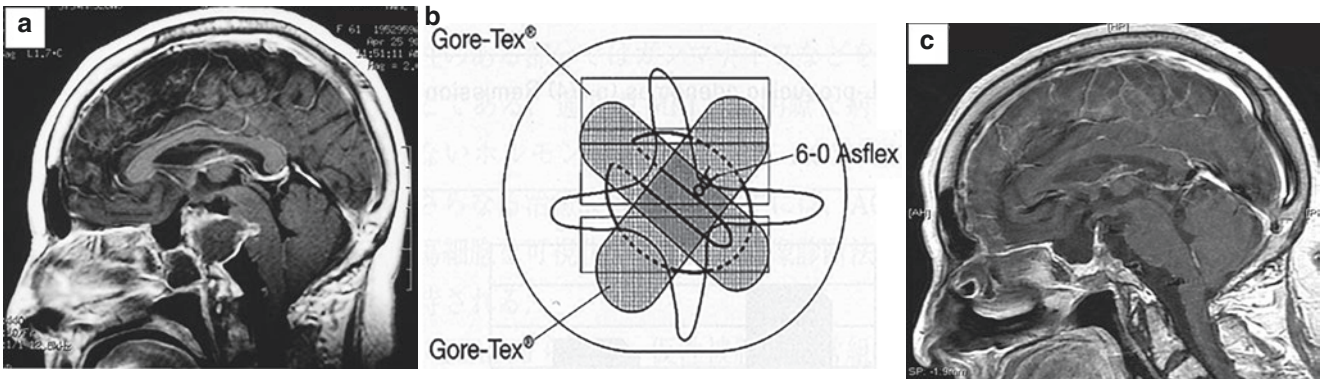

Fig. 1 A 56-year-old woman with craniopharyngioma presented with a headache, hormonal insufficiency, and diplopia. According to our surgical grading system, the tumor was grade III (**a**). Total removal was performed via the transnasal transsphenoidal approach with opening of the clival dura mater. Upon completion of the resection, closing of the dural defect was attained with a specific suturing method using a patch graft of abdominal fascia, as was originally described by the senior author in 1986 (**b**). During the 12 years since the surgery, the patient has experienced no symptoms or signs of hormonal insufficiency, but courses of steroids and mild-intensity replacement therapy for thyroid function have occasionally been necessary. There has been no tumor recurrence or cerebrospinal fluid leakage during follow-up (**c**)

addition, in two patients with a cystic CPH, pure endoscopic procedures were accomplished.

Follow-Up

The mean length of postoperative follow-up in our main surgical group was 121 months (range 6–301 months). Five patients were lost to follow-up; all of them had undergone subtotal tumor resection (STR).

Supplementary Surgical Group and CyberKnife Radiosurgery

In addition to the main surgical group, 17 consecutive adult patients (8 men and 9 women; mean age 54.8 years, range 36–78 years) underwent surgical removal of a CPH via the TTA (in 16 cases) or the AIH approach (in 1 case) between 2012 and 2017. In 6 of them, multisession SRS with the CyberKnife was applied after tumor resection for management of either a small residual neoplasm (in 5 cases) or recurrence of the cystic lesion (in 1 case).

Statistics

Analysis of variance (ANOVA) and nonparametric tests were used for statistical analysis. P values <0.05 were considered statistically significant.

Results

Overall, in the main surgical group, GTR was attained in 81% of cases. It was performed in 84%, 58%, and 85% of patients operated on via the TTA, PA, and AIH approach, respectively ($P > 0.05$). Complete tumor removal was accomplished during the first surgery in 67 cases, but in 14 others, multiple procedures were required to accomplish GTR (two procedures in 10 cases and three in 4 cases). In addition, pure endoscopic surgeries allowed for two-stage total removal of a cystic CPH in a child, but in another patient, who was elderly and had renal failure, only partial tumor removal was done. The main reason for STR of the neoplasm in the present series was a desire to avoid injury to adjacent critical neurovascular structures for prevention of postoperative complications. Neither the initial surgical treatment at another institution nor preoperative GKS demonstrated statistically significant associations with the patient's preoperative Karnofsky Performance Scale (KPS) score or attainment of GTR.

Two patients, who underwent several resections of their neoplasms, died at 7 and 24 months after their last surgery, because of pneumonia in one and endocrinological complications in the other. Two other patients died during the follow-up period as a result of malignant tumors unrelated to their primary disease. All other patients have maintained good quality of life. There was a statistically significant increase in the KPS score ($P < 0.05$) after surgery in comparison with the preoperative period. Neither the initial surgical treatment at another institution nor preoperative GKS demonstrated statistically significant associations with the patient's postoperative KPS score. During follow-up after the surgery, no case of tumor recurrence was noted in cases where GTR of the CPH was accomplished.

In the supplementary surgical group, GTR was attained in 11 of 17 patients (65%). The difference in GTR rates between the supplementary and main surgical groups was not statistically significant ($P > 0.1$).

Clinical and Surgical Correlates of Craniopharyngioma Surgical Grades

According to our surgical grading system for CPH, no patient in our main surgical group had a grade I tumor, 38 had a grade II tumor, 45 had a grade III tumor, 16 had a grade IV tumor, and 1 had a grade V tumor.

The mean age of the patients with CPH of grades II, III, and IV was 36, 35, and 24 years, respectively; the only patient with a grade V tumor was a 1-year-old child. Although there was an evident trend toward higher-grade tumors in younger patients, this difference did not reach statistical significance. Both the pre- and postoperative KPS scores had statistically significant inverse associations ($P < 0.05$) with the tumor grade (i.e., the higher the grade, the lower the KPS score). Also, there was a statistically significant difference ($P < 0.05$) in tumor grades between groups of patients operated on via different surgical approaches. In particular, the tumor grade in patients operated on via the TTA was significantly lower than the grades in patients operated on via the PA or AIH approach. GTR was attained in 87%, 69%, 69%, and 0% of patients with CPH of grades II, III, IV, and V, respectively ($P > 0.05$).

Gamma Knife Radiosurgery

For prevention of tumor regrowth, 13 patients in the main surgical group underwent STR followed by postoperative single-session GKS of a residual lesion. In addition, in our practice, such treatment has occasionally been performed as an alternative to reresection for management of a recurrent CPH after initial incomplete resection. These cases were included in the previous analysis, which has been published elsewhere [16, 17].

CyberKnife Radiosurgery

In all 6 patients in the supplementary surgical group who underwent multisession SRS with the CyberKnife, tumor shrinkage was noted during median follow-up of 20.4 months. Management of a recurrent cystic tumor was not accompanied by its enlargement; in fact, it resulted in complete disappearance of the lesion (Fig. 2). Postoperative pituitary dysfunction lasting >3 months was revealed in 2 of 17 patients (12%) in the supplementary surgical group.

Discussion

Complete tumor removal is the ultimate objective of surgery for a CPH, since it can be considered a curative treatment. In the largest reported series, GTR was attained in 49–90% of cases, with highly variable incidence of surgical complications and postoperative mortality, and resulted in 10-year recurrence-free survival rates of 74–81% [1, 2, 4, 8, 11, 18–23]. For example, Shi et al. [22] reviewed outcomes after surgery for a CPH in 284 patients, including 58 children, who were operated on between 1996 and 2006. Overall, GTR, STR, and partial tumor removal were achieved in 83.5%, 12.9%, and 4.5% of cases, respectively. The early postoperative mortality rate was 4.2%. Out of the total cohort, 204 patients were followed up for between 0.5 and 8 years (mean 2.1 years) after surgery. Tumor recurrence was noted in 14.1% of cases after GTR (within 1–3.5 years) but occurred in 64.9% of patients after STR or partial resection (within 0.25–1.5 years) [22]. In another study, Van Effenterre and Boch [23] performed a retrospective analysis of their 25-year surgical experience in 122 patients with a CPH. Overall, GTR, STR, and partial tumor removal were achieved in 59%, 29%, and 12% of cases, respectively. The surgical mortality rate was 2.5%. Postoperative irradiation was omitted. In total, 117 patients were followed up for a minimum of 2 months after surgery (the mean length of follow-up was 7 years), and 29 of them experienced one or more tumor recurrences within 1–180 months (mean 42 months, median 12 months). This was noted in 13% of cases after GTR, in 33% after STR, and in 69% after partial resection. Management of recurrence with reresection or irradiation was successful in 83% of patients. The actuarial rates of overall survival (OS) at 2, 5, and 10 years after surgery were 95%, 91%, and 83%, respectively [23]. In one of the most recent reports, Morisako et al. [8] highlighted the results of surgery in 72 patients with a CPH operated on between 2000 and 2014. Using a variety of surgical approaches, GTR, near-GTR, and partial tumor removal were achieved in 59.7%, 38.9%, and 1.4% of cases, respectively. There were no postoperative deaths. Early radiation treatment was omitted. During a mean follow-up period of 4.7 years (range 10–189 months), tumor recurrence or regrowth was revealed in 20.8% of cases and was independently associated with the extent of resection and the MIB-1 labeling index.

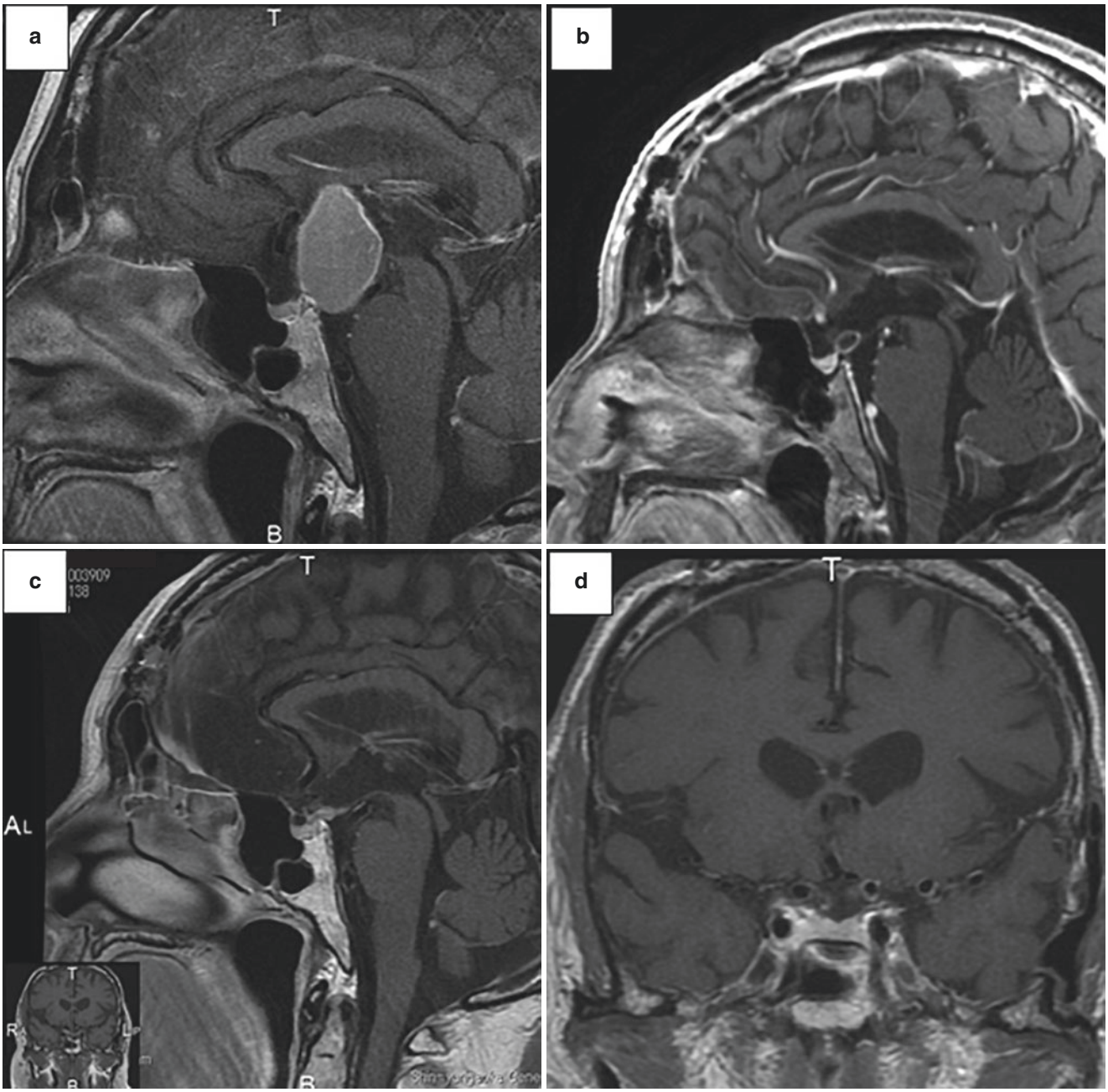

Fig. 2 A 70-year-old man with recurrent craniopharyngioma was initially operated on 20 years earlier at another institution. His neoplasm had been mostly composed of a large cystic component (**a**) and was removed via the anterior interhemispheric trans–lamina terminalis approach. Two years after that surgery, a small recurrence of the cystic tumor was revealed (**b**). Multisession CyberKnife radiosurgery was done and resulted in complete disappearance of the lesion (**c**, **d**). Within 3 years of follow-up, no recurrence of the craniopharyngioma nor any treatment-related complications were noted

It was noted in 9.3% of cases after GTR, 35.7% after near-GTR, and in the one patient who underwent partial tumor removal, and was successfully controlled by a combination of reresection and SRS in 14 of 15 patients [8]. These previously published data are in good concordance with the postoperative results seen in our main surgical group (reported herein), with a GTR rate of 81%, early and late disease-specific postoperative mortality rates of 0% and 2%, respectively, and no cases of recurrence after GTR within the mean postoperative follow-up period of 121 months.

Surgical Classifications and Grading Systems for Craniopharyngiomas

Surgical classification and subgrouping of CPH are absolutely necessary for selection of the optimal surgical approach and the treatment strategy in general, as well as for prediction of the outcome. For instance, in their large series, both Yasargil et al. [11] and Hoffman et al. [4] observed 90% rates of GTR, but the postoperative mortality rates they reported were strikingly different (16.7% versus 2%), which could be explained by the variable patient and tumor characteristics in their cohorts. Thus, for reliable comparison of reported results in different studies and assessment of various treatment modalities (including SRS), uniform evaluation of clinical cases with use of a standard grading scheme is required in the same way as is done, for example, in pituitary tumors, with separation of micro- and macroadenomas, and definition of cavernous sinus invasion according to the Knosp criteria [24].

The main purpose of any surgical classification of CPH is prediction of the interrelationships between the tumor and surrounding structures on the basis of assessment of preoperative factors, which can optimize selection of the surgical approach and estimate postoperative results. At the same time, to gain widespread acceptance, such grading schemes should be based on objective parameters whose evaluation has minimal dependence on the operator, they should be easy to use in order to facilitate routine practical applications, and they should demonstrate clear clinical and surgical associations. Several classification systems for CPH have been proposed previously [2, 4, 7, 8, 10, 11]. For example, Kassam et al. [7] and Yasargil et al. [11] differentiated subtypes of tumors according to intraoperative findings—in particular, considering interrelationships between the lesion and infundibulum. However, even with use of advanced modern neuroimaging, it may sometimes be rather difficult to clarify such microanatomical details preoperatively, which limits the usefulness of the related classifications in selection of the optimal surgical approach. On the other hand, Yamada et al. [10] differentiated supradiaphragmatic CPH according to their relationships with the third ventricle considering both preoperative MRI and intraoperative observations. Their suggested scheme is very simple and straightforward but seemingly applicable only to lesions operated on via the TTA. Recently, Morisako et al. [8] introduced an anatomical subclassification of CPH based on the location, origin, and growth pattern of four tumor types: intrasellar, prechiasmatic, retrochiasmatic, and intra–third ventricle. However, such a discrete subgrouping may not reflect all possible variants of tumor extension.

Our original surgical grading system for CPH may be more advantageous than those suggested previously. First, all evaluated tumor-associated factors can be easily assessed on standard preoperative MRI with minimal subjectivity. Second, it is essentially multiparametric and considers not only the size of the tumor but also its structure. Third, it is suitable for all types of lesion and considers not their individual relationships with adjacent anatomical structures (e.g., the sella turcica, optic chiasm, infundibulum, or third ventricle) but the degree of volumetric extension in the lateral, superior, posterior, and inferior directions, which may carry definite clinical and surgical associations. For example, invasion of the mammillary bodies may be related to memory dysfunction, and obstruction of the foramen of Monro may cause hydrocephalus, whereas extension below the clinoidal line may create problems for complete tumor removal via the TTA or subfrontal approach. Fourth, in contrast to the discrete groupings of neoplasms done by others, we evaluate several tumor-associated parameters that are relevant to resection as a continuous score, which may better reflect the characteristics of the pathological process. Finally, the defined tumor grades have demonstrated statistically significant associations with pre- and postoperative KPS scores. Therefore, the suggested grading system can be potentially helpful during preoperative decision-making as to selection of the optimal treatment strategy, choice of the surgical approach, and determination of the prognosis. Validation of its efficacy should certainly be done in further independent studies.

Gamma Knife Radiosurgery

Our current strategy for management of CPH is directed at GTR or near-GTR with close postoperative clinical and radiological follow-up. However, in 19% and 35% of cases in our main and supplementary surgical groups, respectively, only STR of the lesion was attained. Incomplete removal of CPH results in a 31–42% 10-year recurrence-free survival rate, but this rate increases to 83–100% if surgery is combined with postoperative irradiation of the residual lesion [3, 9, 25, 26]. In such cases, we prefer to use not FRT but SRS, since image-guided, stereotactically navigated, extremely precise, conformal, and selective delivery of high radiation doses with a steep falloff outside the target volume in single or multiple (up to five) sessions not only increases treatment efficacy but also reduces the risk of associated morbidity.

Single-session GKS may be considered a gold standard for SRS of intracranial tumors and has demonstrated its effectiveness in the management of CPH (Table 2) [1, 13, 14,

Table 2 Summary of selected studies on the results of Gamma Knife radiosurgery for craniopharyngiomas

Study	Institution	Number of patients	Tumor volume (cc)	Marginal dose (Gy)	Length of follow-up (months)	Tumor control rate (%)	Tumor shrinkage rate (%)	Tumor enlargement rate (%)
Prasad et al. (1995) [27]	University of Virginia	8[b]	Mean 4.7 (range 0.5–17.0)	Mean 12.4 (range 9–16.7)	Mean 20 (range 6–48)	88	63	37 (Out of 3 progressing lesions, cyst enlargement was noted in 2 and appearance of a new tumor component in 1)
Mokry (1999) [28]	University of Graz	23	Mean 7.0	Mean 10.8 (range 8–15)	Mean 24	78	74	22 (All 5 enlarged tumors had a prominent multicystic component)
Chung et al. (2000) [29]	Taipei Veterans General Hospital	31	Mean 8.9 (range 0.3–28)	Mean 12.2 (range 9.5–16)	Median 33 (range 5–69)	87.2	64.6	12.8 (The control rate was lower in mixed-type tumors than in single-component ones, whether solid or cystic)
Yu et al. (2000) [30]	Navy General Hospital, Beijing	38[b]	Mean 13.5	Range 8–18	Range 6–24	89.5	ND	10.5 (The control rate was slightly lower in mixed-type tumors)
Chiou et al. (2001) [31]	University of Pittsburgh	10 (12 tumors)	Mean 1.7 (range 0.18–5.2)	Median 16.4 (range 12.5–20)	Median 63 (range 13–150)	91.7	75	8.3 (In 5 of 8 tumors with a cystic component, enlargement of it was noted)
Barajas et al. (2002) [32]	Hospital San Javier, Guadalajara	10	Mean 4.5 (range 0.68–14.2)	Mean 14 (range 12.5–17)	Median 33 (range 12–48)	90	90	10 (In only one progressing tumor, enlargement of both solid and cystic components was noted)
Ulfarsson et al. (2002) [33]	Karolinska Hospital	21 (22 tumors)	Mean 7.8 (range 0.4–33)	Mean 5 (range <3–25)	Median 42 (range 6–348)	36.4	22.7	63.6 (Tumor progression was associated with a low prescription dose)
Amendola et al. (2003) [34]	Miami Neuroscience Center	14	Median 3.7 (range 0.1–26.5)	Mean 14 (range 11–20)	Mean 39 (range 6–86)	86	ND	14 (Both progressive tumors were successfully retreated with GKS or FRT)
Albright et al. (2005) [18]	Children's Hospital of Pittsburgh	5	Mean 0.65 (range 0.36–0.98)	ND	Mean 29 (range 3–83)	80	40	20
Kobayashi et al. (2005) [13]; Kobayashi (2009) [14]	Nagoya Kyoritsu Hospital	98[b]	Mean 3.5	Mean 11.5 (range 10.7–12.7)	Mean 65.5 (range 6–148)	79.6	67.3	20.4 (Outcomes were worse in cases of cystic and mixed-type tumors)
Yomo et al. (2009) [16]	Tokyo Women's Medical University	18[b]	Mean 1.8 (range 0.12–13.9)	Mean 11.6 (range 10–14)	Median 24 (range 12–52)	94	72	6 (The control rate was lower in cystic tumors)
Hasegawa et al. (2010) [35]	Nagoya Kyoritsu Hospital	100 (109 tumors)	Median 3.3 (range 0.1–36)	Median 11.4 (range 9.6–18)	Median 68 (range 10–183)	65	ND	35 (39% of infield treatment failures were caused by cyst enlargement)

(continued)

Table 2 (continued)

Study	Institution	Number of patients	Tumor volume (cc)	Marginal dose (Gy)	Length of follow-up (months)	Tumor control rate (%)	Tumor shrinkage rate (%)	Tumor enlargement rate (%)
Niranjan et al. (2010) [36]	University of Pittsburgh	46 (51 tumors)	Median 1.0 (range 0.07–8.0)	Median 13.0 (range 9–20)	Median 32 (range 12–232)	68.6	ND	31.4 (Complete coverage of the entire tumor (including cystic and solid components) with prescription isodose was found to be essential for attainment of local control)
Xu et al. (2011) [37]	University of Virginia	37 (39 tumors)	Median 1.6 (range 0.1–18.6)	Median 14.5 (range 6–25)	Median 50 (range 8–212)	67.5	ND	32.5 (An absence of visual field defects at the time of GKS, a smaller target volume, and a larger prescription dose were independently associated with better local tumor control)
El Khamlichi et al. (2013) [1]	Mohammed V University Souissi, Rabat	6[b]	Mean 6.6 (range 0.2–17.0)	Mean 11 (range 8–14)	>12	100	67	0
Saleem et al. (2013) [38]	Neurospinal and Cancer Care Institute, Karachi	35	Mean 12 (range 1–33.3)	Mean 11.5 (range 8–14)	Mean 22 (range 6–36)	88.6	77.1	11.4 (The rate of local control was lower in mixed-type tumors harboring multiple cysts than in single-component lesions, whether solid or cystic)
Lee et al. (2014) [39]	Taipei Veterans General Hospital	128[b]	Median 5.5 (range 0.2–28.4)	Median 12.0 (range 9.5–16.0)	Median 45.7 (range 6–226)	55.5	53.9	44.5 (The rate of tumor control was slightly lower in mixed-type tumors)
Kobayashi et al. (2015) [40]	Nagoya Kyoritsu Hospital	29[b]	Mean 2.6 (range 0.3–9.3)	Mean 11.7 (range 8.2–23.0)	Median 91 (range 6–120)	89.7	69.0	10.3
Dho et al. (2018) [41]	Seoul National University[a]	35 (40 tumors)	Mean 1.45 (range 0.07–10.82)	Median 15 for single-session GKS; median 6 per session for 3-session GKS	Median 65 (range 12–225)	60	55	40 (A hypothalamic tumor location and greater BED2 were independently associated with a better response to GKS)
Losa et al. (2018) [42]	Vita-Salute University[a]	50	Mean 2.15 (range 0.07–7.96)	Mean 14.9 for single-session GKS; mean 6.9 per session for multisession GKS	Mean 75 (range 6–227)	86	64.3[c]	14 (Solid tumors had a higher response rate than cystic and mixed-type ones)

BED2 biologically effective dose for an α/β ratio of 2 Gy, *FRT* fractionated radiotherapy, *GKS* Gamma Knife surgery, *ND* no data

[a]This series included patients treated with multisession radiosurgery

[b]Patients with available follow-up data

[c]The volumetric response was assessed in 28 of 50 patients (56%) in this series

16, 18, 27–42]. Minniti et al. [43] performed integrated analysis of eight published studies comprising 252 patients who underwent GKS for a CPH with a median follow-up duration of 57 months, and reported an overall tumor control rate of 69%; on average, the tumor control rates were 90%, 88%, and 60% in solid, cystic, and mixed-type lesions, respectively. Fair to excellent clinical outcomes were noted in 73–89% of patients [13, 29, 38, 40]. The treatment effects of GKS are sufficiently durable [13, 14, 31, 39, 40, 44]. Kobayashi et al. [13] analyzed long-term outcome in a series of 98 patients who underwent low-dose irradiation (mean marginal dose 11.5 Gy, range 10.7–12.7 Gy) for a CPH (mean volume 3.5 cc) and were followed up for an average duration of 65.5 months (range 6–148 months) thereafter. At the time of the last follow-up, the tumor control rate was 79.6%; a complete response was noted in 19.4% of cases and a partial response in 48.0%. The actuarial 5- and 10-year progression-free survival (PFS) rates were 60.8% and 53.8%, and the OS rates were 94.1% and 91%, respectively [13]. Similarly, Lee et al. [39] reported the results of GKS for a CPH in 137 consecutive patients; follow-up data were available for 128 of them. The median tumor volume was 5.5 cc (range 0.2–28.4 cc), and the median marginal dose was 12.0 Gy (range 9.5–16.0 Gy). During median follow-up of 45.7 months (range 6–226 months), the tumor control and shrinkage rates were 55.5% and 53.9%, respectively. Local control was achieved in 72.7% of solid CPH, 73.9% of cystic CPH, and 66.3% of mixed-type lesions. The actuarial 5- and 10-year PFS rates were 70.0% and 43.8%, and the OS rates were 91.5% and 83.9%, respectively [39]. Even in the series reported by Ulfarsson et al. [33], who evaluated long-term results in a cohort of the first Swedish patients treated for a CPH with GKS between 1968 and 1995, with a median follow-up duration of 42 months (range 6–348 months), the tumor control and shrinkage rates were 36.4% and 22.7%, respectively, even though this cohort included cases irradiated with a first-generation Gamma Knife without the currently available modalities for high-resolution imaging and computer-assisted treatment planning, and with frequent use of a very low prescription dose (e.g., <6 Gy, which understandably resulted in an 85% recurrence rate). Notably, the reported incidence of treatment-related complications after GKS for a CPH is sufficiently low [25, 44].

The Tokyo Women's Medical University experience with single-session GKS of a CPH has been analyzed previously by Yomo et al. [16, 17]. Their initial study [16] comprised 18 patients with residual or recurrent tumors, with a mean volume at the time of irradiation of 1.8 cc (range 0.12–13.9 cc). The mean marginal dose at the 50% prescription isodose line was 11.6 Gy (range 10–14 Gy). During a median follow-up period of 24 months (range 12–52 months), the tumor control and shrinkage rates were 94% and 72%, respectively. There was a statistically nonsignificant trend ($P = 0.0658$) toward worse tumor control in cystic neoplasms. No complications or adverse effects after GKS were noted. Improvement of visual function accompanied significant tumor shrinkage in three patients [16]. An updated study of the long-term results [17] included 51 patients, in whom the median duration of follow-up after GKS was 71 months (range 1–144 months). The actuarial 3- and 5-year local tumor control rates were 88% and 67%, respectively. Multivariate analysis showed that prior FRT and the presence of a cystic component in the lesion were associated with worse local control. Outfield recurrence was noted in 11% of cases. During follow-up, six patients had deterioration of vision because of tumor progression, but no case of radiation-induced optic neuropathy was noted. New-onset diabetes insipidus was seen in two patients. Overall, 35% of patients needed an additional intervention after GKS. The 5-year OS rate was 92% [17].

Historically, single-session GKS for CPH was limited to tumors with a maximum diameter of ≤3 cm, located at a distance of 3–5 mm from the anterior optic pathways [45, 46]. Indeed, the proximity of the optic nerves and chiasm is the main limiting factor for single-session SRS, and the radiation dose delivered to these structures should be limited to 8–10 Gy to avoid an increased risk of radiation-induced neuropathy, especially in cases that have already undergone previous irradiation [9, 25, 28, 35, 44, 46, 47]. This may create problems for treatment planning in some cases, because to provide effective local tumor control, the prescription dose in CPH cases should not be decreased below 12 Gy [43]. A smaller distance between the tumor and the optic nerve has been noted as an unfavorable prognostic factor for the response to GKS [37, 41]. Nevertheless, multisession GKS, which can be particularly delivered with a Leksell Gamma Knife Icon™ (Elekta AB), has significantly facilitated management of tumors in the vicinity of the anterior optic pathways and other critical neuronal structures. Such treatment can be effectively applied even to relatively large lesions, and its effectiveness may be comparable to that of single-session GKS [41, 42].

CyberKnife Radiosurgery

Both single- and multisession SRS in patients with intracranial tumors may also be effectively performed with use of the CyberKnife. This device consists of a miniature lightweight LINAC mounted on a robotic arm with six degrees of freedom of movement, providing unobstructed access to the entire body [12, 45]. Photon beam irradiation can be delivered with submillimeter accuracy. An image-guided control loop with target-tracking capabilities allows adjustment for patient movements and obviates use of invasive rigid frame

fixation of the head during treatment, which is particularly advantageous in pediatric patients [48]. Instead, immobilization is attained with a thermoplastic mask. This significantly facilitates administration of multisession SRS and hypofractionated stereotactic radiotherapy (SRT), which may be indicated in cases of tumors located in the vicinity of eloquent neurovascular structures (e.g., a CPH), allowing delivery of higher cumulative radiation doses over a longer period of time [9, 12, 25, 45, 48, 49].

Giller et al. [50] reported one of the first large series of pediatric patients who underwent treatment with the CyberKnife for a variety of intracranial tumors, including three CPH. In the latter cases, administration of SRT, with a total dose of 31–50 Gy delivered in 17–25 fractions, resulted in a complete response in two tumors and a partial response in one [50]. However, there have been only a few reports on SRS with the CyberKnife for management of CPH (Table 3) [45, 47, 51]. Lee et al. [45] retrospectively evaluated its results in 11 patients who underwent multisession treatment for residual or recurrent neoplasms. The mean target volume was 6.0 cc (range 0.3–26.3 cc), and the mean marginal dose at the 75% prescription isodose line (range 67–80%) was 21.6 Gy (range 18–38 Gy). When delineation of the anterior optic pathways was possible, their exposure to radiation was limited to <5 Gy per session. No acute complications or side effects were noted. During a mean follow-up duration of 15.4 months (range 4–64 months), tumor control or shrinkage without any neuroendocrine or visual complications was achieved in 10 patients (91%). One cystic tumor increased in volume, but this was not accompanied by neurological signs or symptoms [45]. Iwata et al. [47] retrospectively evaluated results in 43 patients. In 3 cases, single-session SRS was done (median tumor volume 0.5 cc; median marginal dose 14.3 Gy), whereas in 40 others, multisession irradiation was delivered in 2–5 fractions (median tumor volume 2.2 cc; median total marginal dose 21 Gy). During a median follow-up duration of 40 months (range 12–92 months), tumor control and shrinkage were noted in 74% and 37% of cases, respectively. Neoplasms developing infield recurrence were significantly larger (mean volume 6.9 cc versus 2.9 cc; $P = 0.02$). Both symptomatic and transient cyst enlargement were frequently observed. Outfield progression of the CPH was noted in 4 patients (9%). The actuarial 3-year PFS and OS rates were 78% and 100%, respectively. No case of radiation-induced optic neuropathy or brain necrosis was noted. Out of 26 patients who did not require hormone replacement therapy before irradiation, hypopituitarism after SRS was noted only in one (3.8%) [47]. Our experience with multisession SRS with CyberKnife for CPH has been recently updated by Ohhashi et al. [51], who analyzed long-term outcomes in 28 patients treated for residual (in 25 cases) or recurrent (in 3 cases) tumors after initial microsurgical resection. Median target volume was 6.2 cc (range, 1.75–14.7 cc). The marginal dose varied from 20 to 25.5 Gy and was delivered in 3–8 fractions. Cyst enlargement accompanied by visual deterioration, which required surgical intervention, was observed soon after SRS in 2 patients with recurrent tumors. However, in another patient described in the present report, recurrent cystic CPH did not show even transient enlargement after irradiation and demonstrated complete response with time. One patient who underwent irradiation for residual tumor died of pneumonia and adrenal insufficiency at 6 years after treatment. Overall, during prolonged follow-up (mean 80 month, range 61–129 months), no tumor regrowth was seen in any case and no complications of SRS were observed. No case of visual impairment was noted. The pituitary function gradually improved in many patients, and never demonstrated deterioration [51].

These results indicate the important role of multisession SRS and hypofractionated SRT with the CyberKnife in the management of residual and recurrent CPH, advocate widespread application of these treatment modalities, and warrant their further evaluation in additional clinical studies. Of particular interest may be combined use of conservative surgery for CPH followed by early irradiation of the residual tumor with the CyberKnife, since such treatment strategy may yield highly beneficial oncological and functional outcomes [51].

Comparison of Gamma Knife and CyberKnife Radiosurgery

Timmerman et al. [52] outlined three requirements for successful SRS: (1) ability to define the location of the target volume, (2) ability to shape the prescription isodose to the surface of the target volume, and (3) ability to construct radiation dose distributions with a very rapid falloff outside the target volume to spare surrounding healthy tissue. All of these objectives can be effectively achieved with currently existing equipment for SRS with both the Gamma Knife and CyberKnife, and seemingly neither method is more advantageous than the other with regard to radiation delivery and dosimetry. Moreover, both techniques provide good options for multisession SRS and, given the current technological advances in image guidance, such treatment can be performed with very high conformity and selectivity, providing additional options in cases of large or critically located lesions, such as a CPH immediately adjacent to the anterior optic pathways [9, 12, 45]. Indeed, the risks of visual loss and pituitary or hypothalamic dysfunction after multisession SRS for perioptic tumors appear to be low [12, 45, 47, 53].

To evaluate the tumor response to irradiation, we compared the results of selected studies on SRS for CPH (see Tables 2 and 3). In 15 selected series of patients who underwent GKS [1, 13, 16, 18, 27–29, 31–33, 38–42], tumor

Table 3 Summary of selected studies on the results of CyberKnife radiosurgery for craniopharyngiomas

Study	Institution	Number of patients	Tumor volume (cc)	Marginal dose (Gy)	Length of follow-up (months)	Tumor control rate (%)	Tumor shrinkage rate (%)	Tumor enlargement rate (%)
Lee et al. (2008) [45]	Stanford University[a]	11[c]	Mean 6.0 (range 0.3–26.3)	Mean 21.6 (range 18–38) delivered in 3–10 sessions	Mean 15.4 (range 4–64)	91	64	9 (Enlargement was seen in one cystic tumor)
Iwata et al. (2012) [47]	Nagoya City University[b]	43	Median 2.0 (range 0.09–20.8)	Median 14.3 for single-session SRS; median 21 for multisession SRS	Median 40 (range 19–92)	74	37	26 (Tumors developing infield recurrence had significantly larger volumes; cyst enlargement was frequently observed)
Ohhashi et al. (2020) [51]	Shin-Yurigaoka General Hospital	28[d]	Median 6.2 (range 1.75–14 .7)	From 20.0 to 25.5 delivered in 3–8 sessions	Mean 80 (range 61–129)	100	ND	7 (Cyst enlargement was seen in 2 recurrent tumors soon after SRS and required surgical intervention)

ND no data, *SRS* stereotactic radiosurgery

[a]This series included 1 patient treated with hypofractionated stereotactic radiotherapy

[b]This series included 3 patients treated with single-session radiosurgery

[c]Patients with available follow-up data

[d]This updated series included some patients described in the present report

shrinkage was noted in 306 of 493 cases (62%). In two previously published reports on SRS with the CyberKnife [45, 47] and six of our patients presented herein, tumor shrinkage was noted in 29 of 60 cases (48%). Although the difference reached statistical significance ($P < 0.05$), it may have been biased by disproportionate case numbers and different tumor sizes, with larger lesions being selected for multisession SRS. Enlargement of a cystic CPH after irradiation was consistently reported with use of any method but does not necessarily indicate treatment failure and tumor progression (in particular, if it occurs during the first year of follow-up), since it may be self-limiting and transient; thus, such patients may be observed unless additional treatment is definitely required for major aggravation of symptoms [54, 55].

Given all of these data, it remains largely unknown whether GKS or SRS with the CyberKnife provides greater effectiveness and/or safety in patients with a CPH, and possible use of both techniques should be reasonably considered for management of residual tumors if surgery does not result in GTR, or in cases of recurrent neoplasms. The possible benefits of multisession SRS in comparison with single-session irradiation should be established in further studies, preferably performed according to standard treatment protocols in a prospective fashion, and involving large numbers of patients with available long-term follow-up data [43, 45, 46]. Finally, it may be worth trying to apply our original surgical grading system for CPH in cases treated with SRS, since it reflects parameters associated with the response to irradiation—namely, the tumor size, structure, and location.

Conclusion

Complete tumor removal is the preferred management option for a CPH. Selection of the optimal treatment strategy, choice of the surgical approach, and prediction of the outcome should be based on multifaceted analysis of the lesion size, structure, and extension. For this purpose, an original surgical grading system developed at Tokyo Women's Medical University may be quite useful because of its ease of application, clarity, efficacy, and definite clinical and surgical correlates. It can also be helpful for comparison of treatment results in different clinical series and between various treatment modalities—in particular, SRS. The latter has shown good effectiveness in management of small residual or recurrent CPH. Although single-session GKS represents the gold standard in such cases, use of the CyberKnife—in particular, in multisession mode—may provide comparable results with regard to both tumor response rates and treatment safety.

Conflict of Interest The authors have no conflict of interest concerning the reported materials or methods.

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Gamma Knife Radiosurgery for Pituitary Adenomas Invading the Cavernous Sinus: Tokyo Women's Medical University Experience

Motohiro Hayashi, Mikhail F. Chernov, Ayako Horiba, Noriko Tamura, Kosaku Amano, and Takakazu Kawamata

Abstract Total surgical removal of a pituitary adenoma (PA) invading the cavernous sinus (CS) is challenging and carries a significant risk of postoperative complications. As an alternative treatment strategy, after incomplete resection, such tumors may undergo stereotactic radiosurgery—in particular, Gamma Knife surgery (GKS). Treatment planning based on advanced neuroimaging (e.g., thin-slice 3-dimensional postcontrast constructive interference in steady state (CISS) images) allows clear visualization of the target microanatomy, which results in highly conformal and selective radiation delivery to the lesion with preservation of adjacent functionally important neurovascular structures. In the Tokyo Women's Medical University experience of GKS for 43 nonfunctioning and 46 hormone-secreting PA invading the CS, with a minimum follow-up period of 5 years (mean 76 months, range 60–118 months), the tumor control rate has reached 97%, and a significant volume reduction (≥50%) has been seen in 24% of lesions. In cases of hormone-secreting neoplasms, normalization (in 18 patients; 39%) or improvement (in 22 patients; 48%) of endocrinological function has been noted. Importantly, such effects have been sufficiently durable. Complications have been extremely rare and limited to transient cranial nerve palsy (in 2% of cases). Notably, no patient in our series has had a new pituitary hormone deficit after irradiation. Thus, subtotal resection followed by GKS may be considered a valuable alternative to aggressive surgery for a PA invading the CS.

Keywords Cavernous sinus · CISS imaging · Gamma Knife radiosurgery · Invasion · Knosp grade · Outcome · Pituitary adenoma · Radiosurgical treatment planning · Stereotactic radiosurgery

Introduction

A pituitary adenoma (PA) is one of the most common benign intracranial tumors. Its primary management is generally attained with surgery, usually utilizing the transnasal transsphenoidal approach (TTA; also known as the Hardy approach), which is particularly indicated in cases of intra- and suprasellar lesions, with the goal of gross total resection (GTR) [1–4]. However, total removal of a PA extending into the cavernous sinus (CS), especially corresponding to Knosp grade 4 (i.e., with total encasement of the intracavernous internal carotid artery (ICA) [5]), is challenging and carries a significant risk of postoperative morbidity (e.g., diplopia due to injury of the oculomotor and/or abducent nerves). On the other hand, the presence of a residual tumor may result in its regrowth with development of neurological symptoms caused by compression of adjacent neurovascular structures. In addition, incomplete resection of a hormone-secreting PA does not allow normalization of endocrinological function.

As an alternative treatment strategy, benign skull base neoplasms may undergo stereotactic radiosurgery (SRS), including Gamma Knife surgery (GKS), which is now

M. Hayashi (✉)
Faculty of Advanced Techno-Surgery and Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

Saitama Gamma Knife Center, Sanai Hospital, Saitama, Japan
e-mail: gkrmoto@gmail.com

M. F. Chernov
Faculty of Advanced Techno-Surgery and Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

A. Horiba · N. Tamura · K. Amano · T. Kawamata
Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*, Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_4,

widely regarded as a highly effective and safe treatment modality [6–13]. The Tokyo Women's Medical University experience with GKS for a residual or recurrent PA invading the CS is reviewed herein.

Imaging for Evaluation of Cavernous Sinus Microanatomy

Our current concept of GKS for benign skull base tumors (designated as "robotic microradiosurgery") is based on three main principles: (1) very precise irradiation of the lesion with regard to conformity and selectivity; (2) intentional avoidance of excessive irradiation of functionally important anatomical structures, particularly the cranial nerves located both within and in proximity to the target; and (3) delivery of sufficient radiation energy to the tumor to attain its shrinkage, while using a relatively low marginal dose for prevention of possible complications [14–16]. Obviously, realization of such treatment principles requires detailed evaluation of the microanatomy of the target area, which is attained with advanced neuroimaging.

Conventional magnetic resonance imaging (MRI)—mainly various modifications of high-resolution thin-slice postcontrast T1-weighted sequence—plays a major role in diagnosis of a PA and assessment of its extension [17]. However, it does not allow detailed evaluation of the interrelationships between the tumor within the CS and adjacent neurovascular structures—in particular, cranial nerves—which is required for precise radiosurgical treatment planning [16]. Therefore, our group has developed an original neuroimaging protocol for GKS of skull base lesions, based on utilization of thin-slice (thickness 0.5 mm) three-dimensional (3D) plain and postcontrast constructive interference in steady state (CISS) images (heavily T2-weighted MRI), allowing clear identification and delineation of the pituitary stalk and gland, intracavernous cranial nerves, ICA, Meckel's cave, etc. [18, 19]. Additionally, we consistently perform axial thin-slice "bone window" computed tomography (CT) for evaluation of bony structures and estimation of MRI distortion artifacts [14–16].

Advantages of CISS Images

Plain 3D heavily T2-weighted imaging, including CISS sequencing, is widely used for evaluation of lesions within or adjacent to the cerebral ventricles and subarachnoid cisterns. In particular, Xie et al. [20] demonstrated the superiority of this technique on 3T MRI to standard postcontrast T1- and T2-weighted imaging for preoperative delineation of the optic nerves and chiasm, oculomotor nerve, pituitary stalk, and adjacent arteries in cases of sellar tumors. High-resolution CISS images may be effectively used for evaluation of the oculomotor nerve anatomy—in particular, along its intracavernous course within the oculomotor cistern [21]. In addition, heavily T2-weighted imaging may be extremely valuable for identification of CS invasion by a PA. On conventional MRI, such tumor growth may be strongly suspected in cases of total encasement of the intracavernous ICA by the lesion but may be less effectively identified at earlier stages [17, 22]. Evaluation of the borders of the blood pool that normally presents between the intracavernous ICA and the medial wall of the CS may be somewhat helpful, but its obliteration sometimes results from the mass effect of a PA with lateral displacement of the dural wall without its true invasion [17]. On the other hand, in a retrospective study directed at preoperative identification of CS invasion in 98 patients with a PA, Lang et al. [22] found that Knosp grades determined with CISS images correlated with intraoperative findings significantly better than those determined with postcontrast T1-weighted MRI and had superior resolution due to easier visualization of the ICA and dural borders.

Nevertheless, the effectiveness of plain heavily T2-weighted imaging for detailed assessment of the neuroanatomy in the vicinity of skull base tumors, especially large ones or those located within the strictly confined anatomical space, may be limited [18, 19]. This problem can be effectively resolved by administration of a contrast medium, whose accumulation in the neoplasm, as well as in the normal pituitary gland and the CS itself, results in moderate prolongation of their signal and approximates it to that of cerebrospinal fluid but, at the same time, does not significantly affect the intensity of the signal from adjacent neuronal structures [14, 18, 19, 23, 24]. Yagi et al. [23, 24] evaluated identification of the intracavernous cranial nerves in both normal and pathological conditions and demonstrated significantly greater effectiveness of postcontrast 3D CISS images than postcontrast T1-weighted MRI. This corresponds well to our own experience with such a technique, which has allowed visualization and delineation of the entire course of the oculomotor and abducent nerves from their cisternal part till they enter the superior orbital fissure toward the orbital apex (Figs. 1 and 2).

Radiosurgery Treatment Planning

Evaluation of thin-slice CISS images within Leksell GammaPlan® (LGP) (Elekta AB; Stockholm, Sweden), which is dedicated software for GKS and related dosimetry, allows clear visualization and precise delineation of the tumor and adjacent neurovascular structures—in particular, the cranial nerves—within the target area, thus significantly

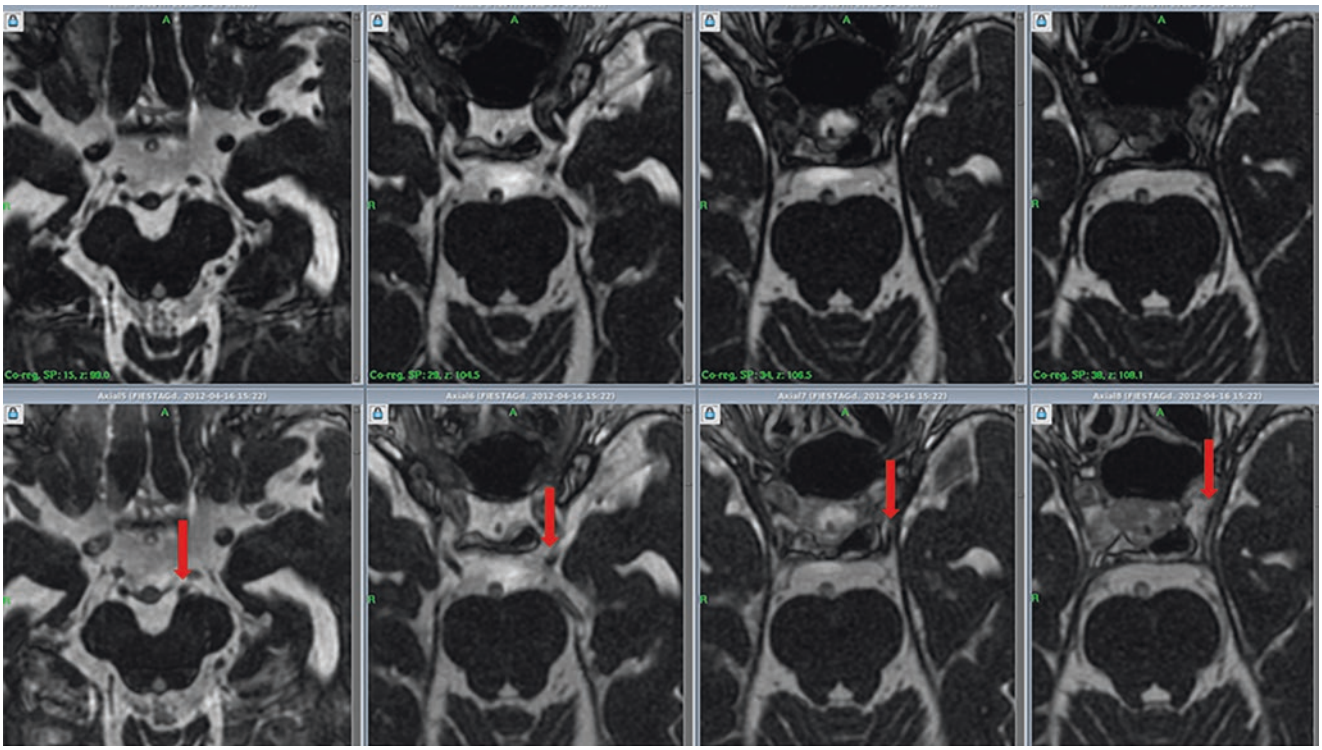

Fig. 1 The Leksell GammaPlan® workspace, displaying axial plain (*upper row*) and postcontrast (*lower row*) three-dimensional (3D) constructive interference in steady state (CISS) images, which allow clear visualization of the oculomotor nerve (*arrows*) during its course within the interpeduncular cistern and, after it enters the porus of the oculomotor cistern, within the lateral wall of the cavernous sinus toward the superior orbital fissure

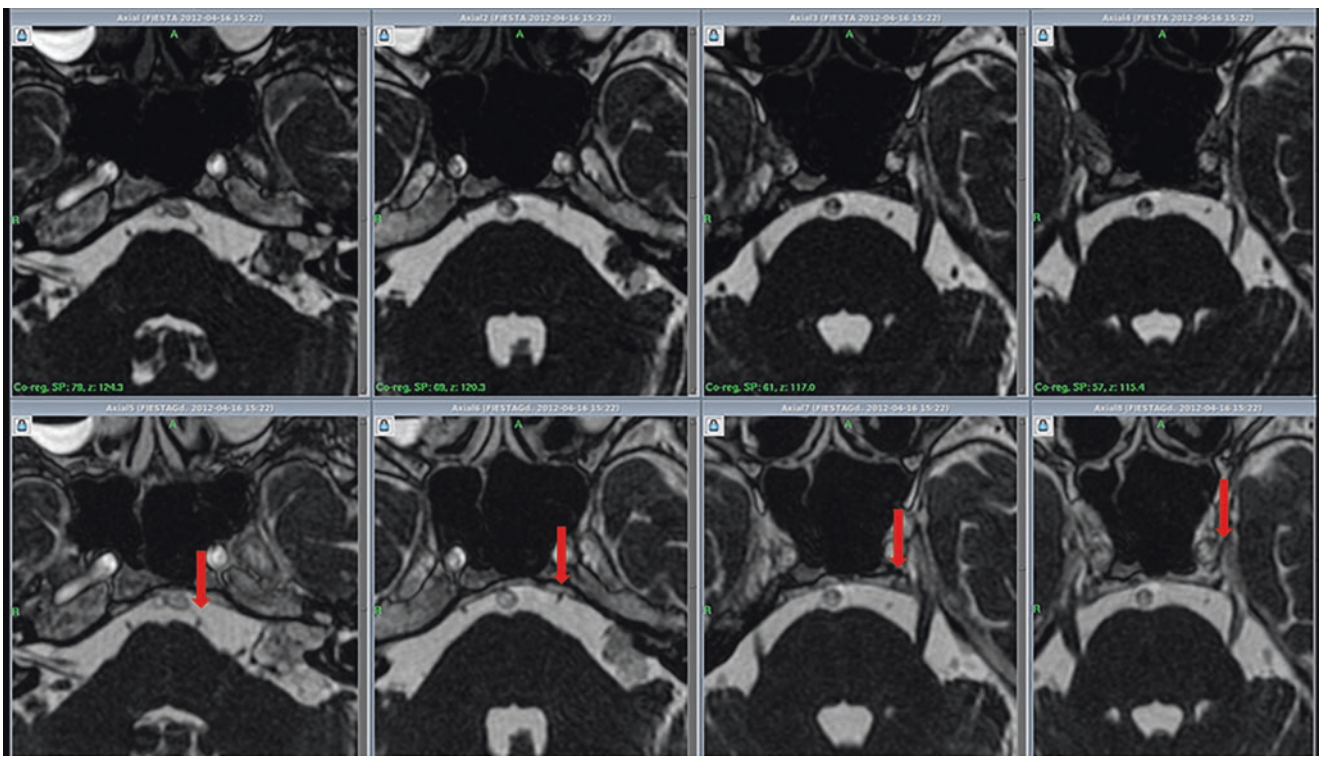

Fig. 2 The Leksell GammaPlan® workspace, displaying axial plain (*upper row*) and postcontrast (*lower row*) three-dimensional (3D) constructive interference in steady state (CISS) images, which allow clear visualization of the abducent nerve (*arrows*) during its course within the prepontine cistern and, after it enters the Dorello canal, within the cavernous sinus inferolateral to the internal carotid artery

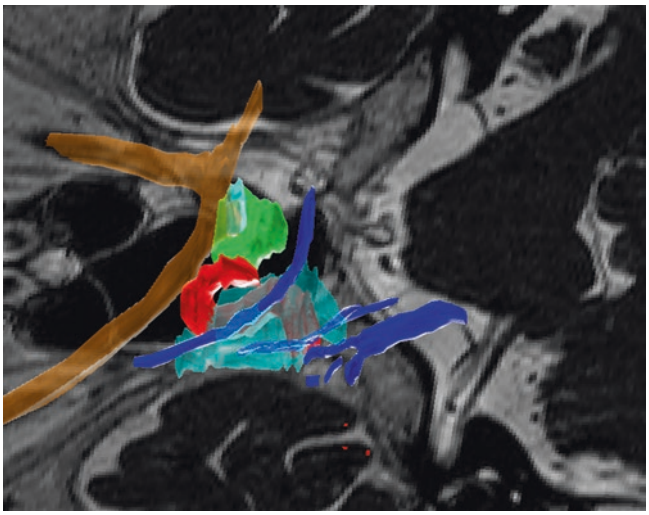

Fig. 3 Use of Leksell GammaPlan® for three-dimensional visualization of the microanatomy of the left cavernous sinus (*light blue*), the adjacent optic nerves and chiasm (*orange*), the internal carotid artery (*red*), the pituitary stalk (*cyan*) and gland (*green*), and cranial nerves III, V, and VI (*blue*)

facilitating 3D understanding of the local neuroanatomy (Fig. 3). Additional coregistration and fusion of "bone window" CT and MR images permit simultaneous visualization of bones and soft tissues, as well as assessment and possible correction of MRI distortion artifacts [14–16]. Analysis of the various images within LGP may also provide clues for identifying the tumor origin and estimating the gradual expansion of the lesion and the type of its growth with or without invasion of surrounding structures. It may allow prediction of the direction of the shift and the position of adjacent cranial nerves, if they cannot be visualized directly (which is not uncommon in tumors invading the CS [24]). In such cases, subsequent radiosurgical treatment planning can be defined as "4D" (i.e., 3D plus the time component).

In our practice, radiosurgical treatment planning for benign skull base tumors is based on use of multiple small-sized isocenters, which are positioned compactly within the borders of the mass [14–16]. As it is typical for GKS, a 50% prescription isodose is usually applied at the margin of the neoplasm, since it provides the steepest radiation dose falloff and optimal gradient index [1]. The prescription dose depends on the lesion volume, the proximity of functionally important neurovascular structures, and previous treatment with SRS or fractionated radiotherapy (FRT). In general, for a nonfunctioning PA, a marginal dose as low as 12 Gy may be quite effective, but for hormone-secreting tumors, it should preferably be ≥20 Gy. The conformity and selectivity indices are usually kept at >0.95 and >0.90, respectively [16]. Since our experience has demonstrated that shrinkage of benign intracranial neoplasms after GKS may be directly associated with the amount of radiation energy that is delivered, we are consistently trying to attain more homogeneous dose distribution and to increase the average dose within the lesion by creating a wide 80% prescription isodose area while maintaining a sufficiently low marginal dose, thus keeping the homogeneity index (the ratio of the target volumes covered by the 80% and 50% prescription isodoses) at ≥0.5 [15, 16]. As was demonstrated in an experimental study performed by Massager et al. [25, 26], the presence of a "hot spot" within the tumor is more likely to provide the desired radiobiological outcome after GKS but does not increase the risk of complications if the dose delivery is sufficiently selective.

Although it is widely accepted that the oculomotor, trochlear, and abducent nerves may safely tolerate doses of up to 30–40 Gy [13, 27], we place special emphasis on avoidance of their excessive irradiation. Therefore, if they are located within the target, in cases of a nonfunctioning PA, the treatment plan is created in such a way that the cranial nerves remain uncovered by the high-dose area. If the cranial nerves cannot be visualized, excessive irradiation of the region where they would presumably be located (e.g., the lateral wall of the CS) is intentionally avoided. In addition, we try to avoid coverage of the ICA with the 80% isodose area (particularly, in younger patients) to prevent radiation injury of the vessel walls. In our practice, the maximal doses delivered to the anterior visual pathways and the brain stem are consistently kept below 10 and 14 Gy, respectively [14–16].

Clinical Results

High effectiveness of SRS in management of PA invading the CS has been demonstrated in multiple studies [1, 6–10, 12, 28], including our own ones [14, 15, 29, 30]. In these series, the tumor control rate varied from 83% to 100% (mean 95% [1]), shrinkage of the lesion was seen in 13–100% of cases, and normalization of endocrinological function was noted during follow-up in 18–88% of patients with a hormone-secreting PA. Improvement of pre-existing neurological symptoms is not uncommon [1, 6, 9]. Nowadays, the treatment-related morbidity has usually been minimal and transient, although mild acute toxicity; hypopituitarism; hyperprolactinemia; optic neuropathy; palsy of cranial nerves III, IV, and VI; blepharoptosis; radiation-induced brain injury; stenosis or occlusion of the intracavernous ICA; aneurysm formation; and development of a secondary malignant tumor have been reported [1, 6, 9–13, 27, 31–38].

Our series of 89 patients who underwent GKS for a PA invading the CS has been described in detail previously [14, 15]. In brief, this treatment was performed for 77 residual and 12 recurrent tumors after initial surgical resection (mainly through the TTA). There were 43 nonfunctioning and 46 hormone-secreting PA; the latter group mainly presented as growth hormone (GH)–secreting tumors (in 25 cases), adrenocorticotropic hormone (ACTH)–secreting tumors (in 13 cases), and prolactin-secreting tumors (in 4 cases). The marginal dose varied from 12 to 25 Gy (mean 18.2 Gy) in nonfunctioning PA and from 12 to 35 Gy (mean 25.2 Gy) in hormone-secreting ones. Control of tumor growth was attained in 86 cases (97%). Reductions of ≥10% and ≥50% in the lesion volume were achieved in 57 cases (64%) and 21 cases (24%), respectively. All three recurrences were noted in ACTH-secreting PA and were treated with repeat GKS. In patients with hormone-secreting PA, the endocrinological function was normalized (in 18 cases; 39%) or improved (in 22 cases; 48%) during postradiosurgery follow-up. Treatment-associated morbidity was noted in 2% of patients and was limited to transitory oculomotor and abducent nerve palsy (in one case each). No patient exhibited a new pituitary hormone deficit after GKS [14, 15]. Of note, there were no substantial changes in these previously reported results with updated follow-up data (mean follow-up duration 76 months, range 60–118 months, versus mean 36 months, range 24–76 months, in our previous report [14]), confirming the safety of GKS and the durability of its treatment effects. Moreover, with extended follow-up, the number of patients with normalization or improvement of endocrinological function increased slightly (87% versus 80%, $P = 0.2501$, according to the McNemar test).

Illustrative Case 1

A 57-year-old woman was diagnosed with a nonfunctioning PA, which caused bitemporal hemianopsia. No other neurological symptoms were noted. Tumor removal was done through the TTA, but a residual neoplasm was left within the right CS. The postoperative period was uneventful; regression of the visual field defect was noted soon after surgery, and there were no new neurological deficits or subjective symptoms. GKS of the residual intracavernous tumor was planned. Postcontrast T1-weighted MRI clearly demonstrated the lesion but did not allow precise evaluation of its interrelationships with adjacent anatomical structures—in particular, cranial nerves. Nevertheless, postcontrast 3D CISS images showed posterior–superior extension of the PA and contact of the tumor with the oculomotor nerve but not with the abducent nerve. Use of this imaging during radiosurgical treatment planning allowed complete coverage of the tumor, with a 14 Gy marginal dose delivered at the 50% isodose line, and prevention of excessive irradiation of the oculomotor nerve (Fig. 4).

Illustrative Case 2

A 43-year-old man was diagnosed with a nonfunctioning PA, which caused bitemporal hemianopsia and diplopia due to palsy of the right abducent nerve. No other neurological symptoms were noted. Tumor removal was done through the TTA, but a residual neoplasm was left within the right CS. The postoperative period was uneventful, the preexisting neurological deficits regressed soon after surgery, and there were no new symptoms or signs. GKS of the residual intracavernous tumor was planned. Postcontrast T1-weighted MRI clearly demonstrated the lesion but did not allow precise evaluation of its interrelationships with adjacent anatomical structures—in particular, cranial nerves. Nevertheless, postcontrast 3D CISS images showed posterior–inferior extension of the PA toward the basilar venous plexus and contact of the tumor with the abducent nerve but not with the oculomotor nerve. Use of this imaging during radiosurgical treatment planning allowed complete coverage of the lesion, with a 14 Gy marginal dose delivered at the 50% isodose line, and prevention of excessive irradiation of the abducent nerve (Fig. 5).

Illustrative Case 3

A 28-year-old woman with an ACTH-secreting PA presented with Cushing disease without any accompanying neurological deficits. Tumor removal was done through the TTA, but a residual neoplasm remained within the left CS. The postoperative period was uneventful, and there were no new symptoms or signs. GKS of the intracavernous neoplasm was planned. Postcontrast T1-weighted MRI demonstrated wide invasion of the left CS by the neoplasm but did not clearly show the borders of the lesion and adjacent cranial nerves. The resolution of postcontrast 3D CISS images was much better, revealing contact of the tumor with the left abducent nerve. Use of this imaging for radiosurgical treatment planning resulted in good coverage of the lesion, with a 20 Gy marginal dose delivered at the 50% isodose line (Fig. 6).

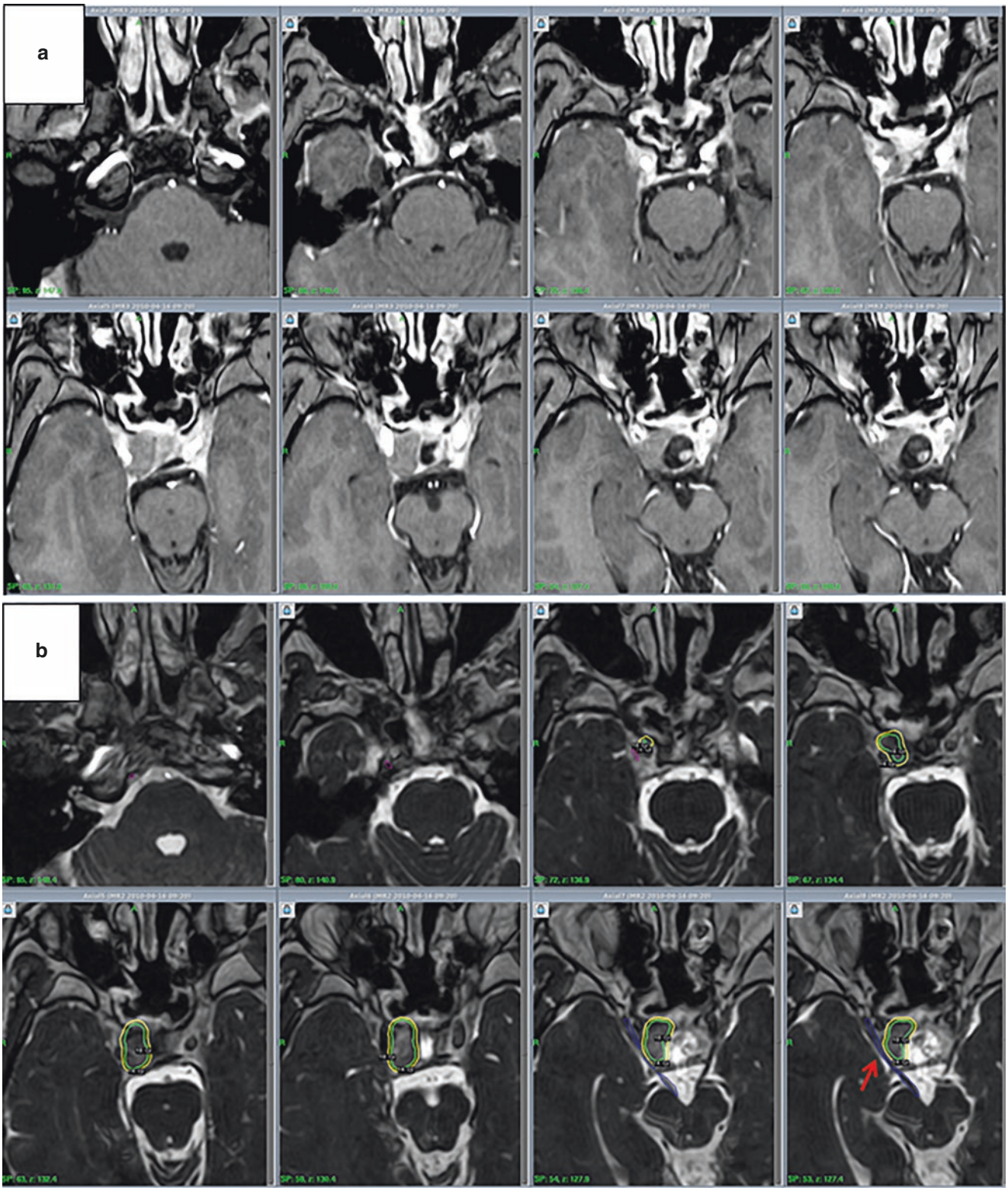

Fig. 4 Residual nonfunctioning pituitary adenoma within the right cavernous sinus in a 57-year-old woman. On postcontrast T1-weighted magnetic resonance imaging (**a**), the lesion demonstrated relatively low signal intensity, but adjacent cranial nerves could not be visualized. At the same time, postcontrast three-dimensional (3D) constructive interference in steady state (CISS) imaging (**b**) clearly showed contact (*arrow*) of the tumor with the adjacent oculomotor nerve (*blue*) and allowed highly conformal and selective radiosurgical treatment planning, with delivery of a 14 Gy marginal dose at the 50% isodose line (*yellow circle*), preventing excessive irradiation of the oculomotor nerve. Note the wide distribution of the 80% isodose area (*green*) within the target

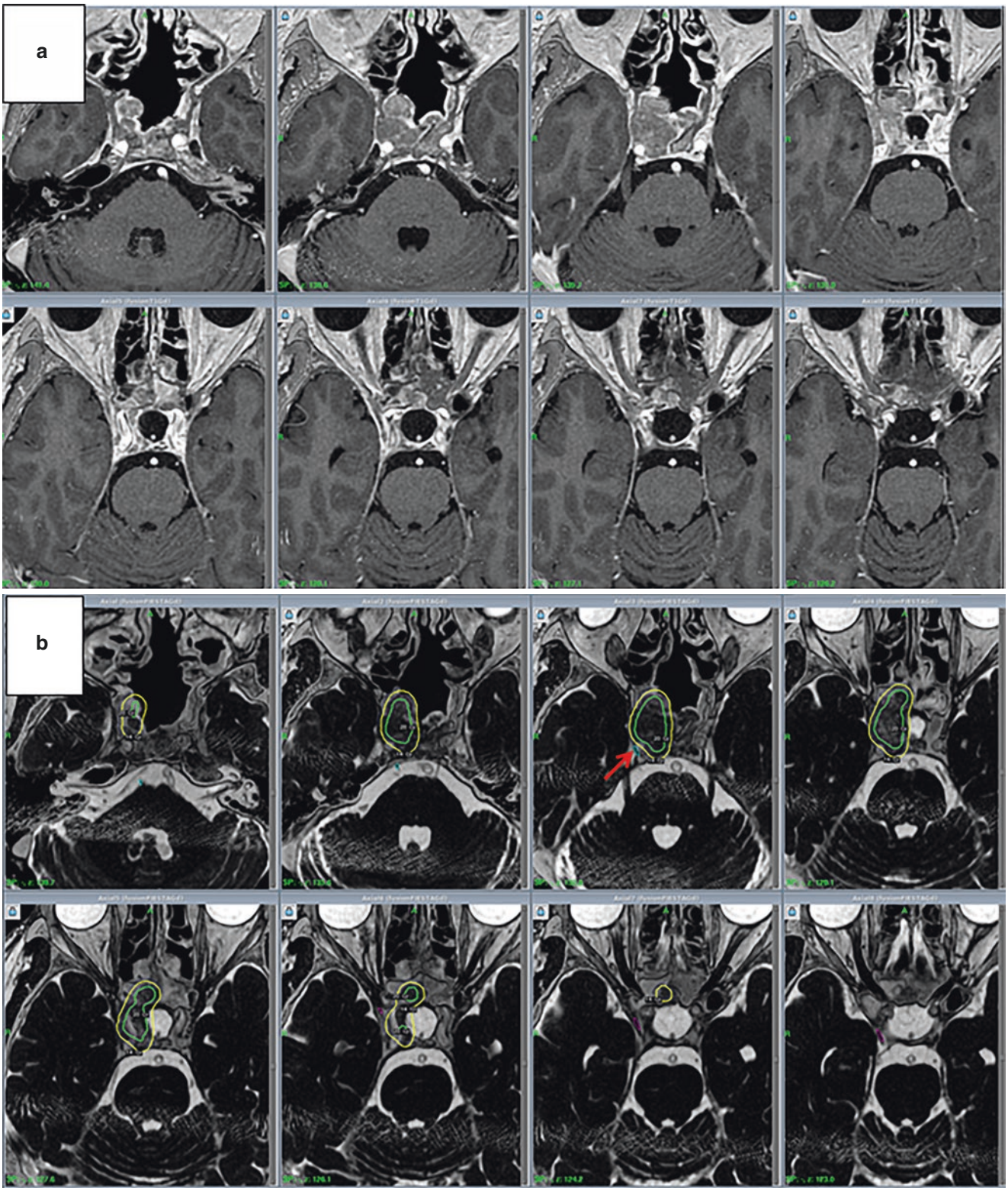

Fig. 5 Residual nonfunctioning pituitary adenoma within the right cavernous sinus in a 43-year-old man. On postcontrast T1-weighted magnetic resonance imaging (**a**), the lesion demonstrated relatively low signal intensity, but adjacent cranial nerves could not be visualized. At the same time, postcontrast three-dimensional (3D) constructive interference in steady state (CISS) images (**b**) clearly showed contact (*arrow*) of the tumor with the adjacent abducent nerve (*light blue*) and allowed highly conformal and selective radiosurgical treatment planning, with delivery of a 14 Gy marginal dose at the 50% isodose line (*yellow circle*), preventing excessive irradiation of the abducent nerve. Note the wide distribution of the 80% isodose area (*green*) within the target

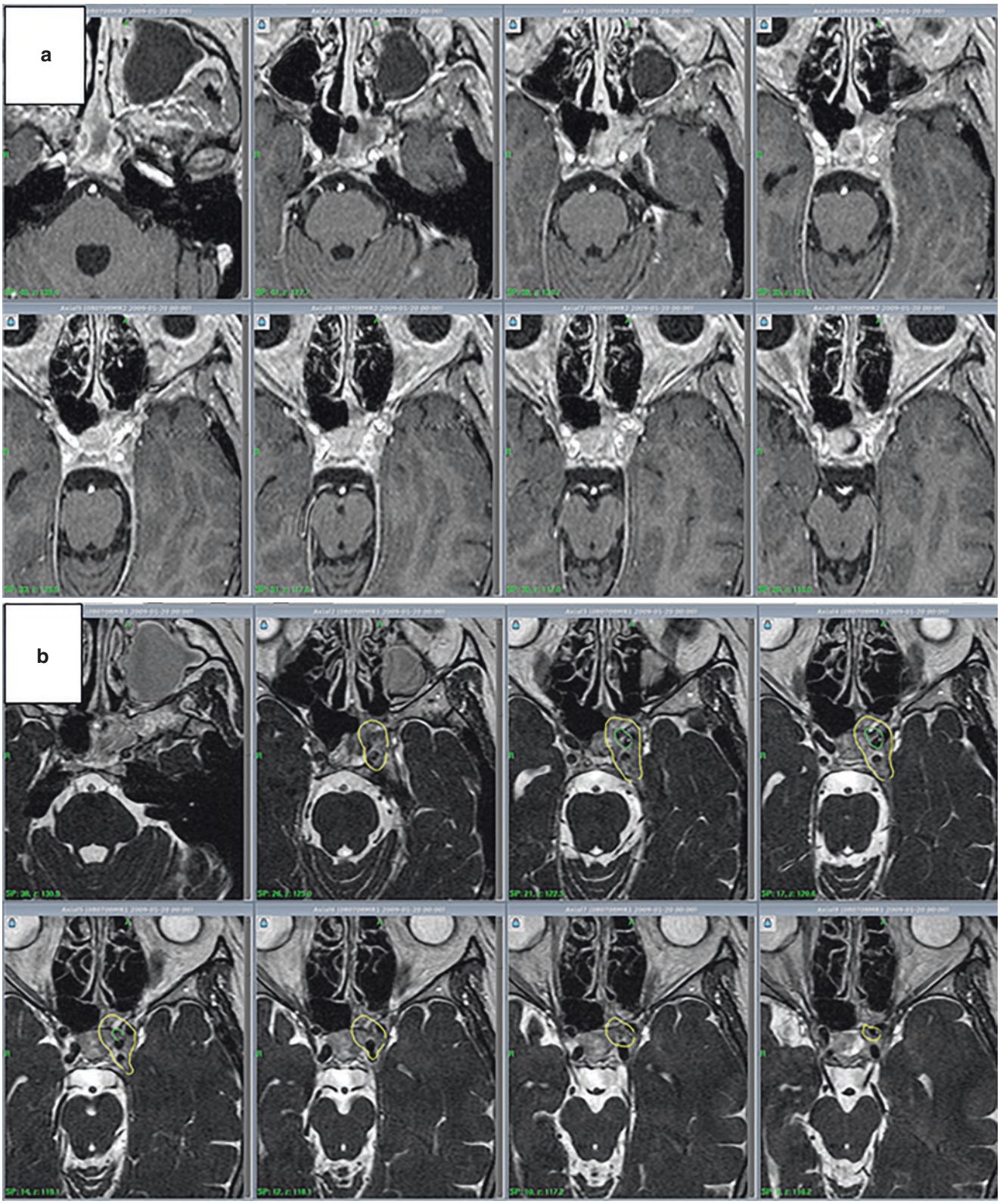

Fig. 6 Residual adrenocorticotropic hormone (ACTH)–secreting pituitary adenoma within the left cavernous sinus in a 28-year-old woman. On postcontrast T1-weighted magnetic resonance imaging (**a**), the borders of the lesion and adjacent cranial nerves could not be seen clearly. Therefore, radiosurgical treatment planning was based on postcontrast three-dimensional (3D) constructive interference in steady state (CISS) images (**b**), which allowed sufficiently conformal and selective delivery of a 20 Gy marginal dose at the 50% isodose line (*yellow circle*). The distribution of the 80% isodose area (*green*) within the target is also defined

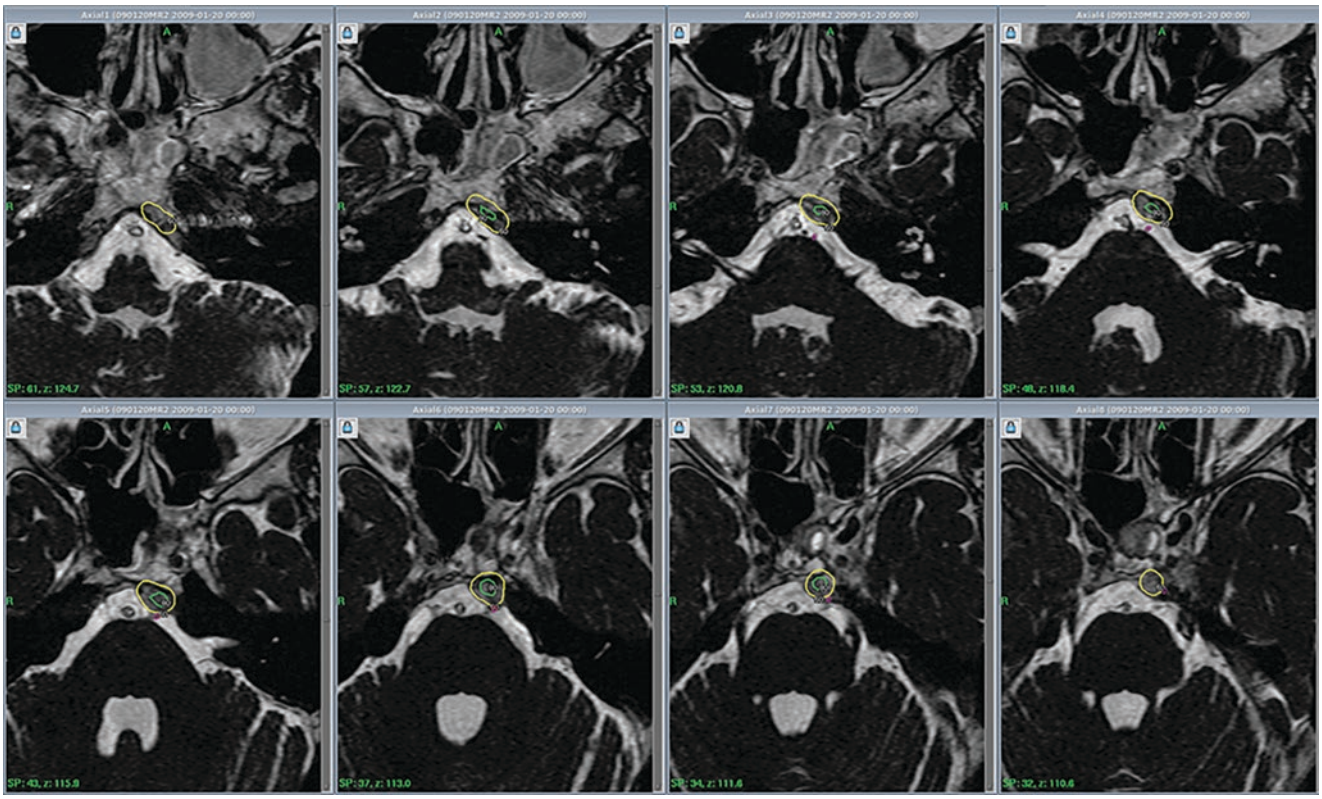

Fig. 7 Treatment plan based on postcontrast three-dimensional (3D) constructive interference in steady state (CISS) images at the time of the second Gamma Knife radiosurgery for regrowth of an adrenocorticotropic hormone (ACTH)–secreting pituitary adenoma manifesting with progressive diplopia due to palsy of the left abducent nerve. The tumor was covered with a 20 Gy marginal dose delivered at the 50% isodose line (*yellow circle*), preventing excessive irradiation of the abducent nerve (*red*). The distribution of the 80% isodose area (*green*) within the target is also defined

Nevertheless, progressive diplopia developed within 1 year after the treatment, and MRI demonstrated tumor regrowth with compression of the left abducent nerve. Repeat GKS based on the postcontrast 3D CISS images was done with delivery of a 20 Gy marginal dose at the 50% isodose line, preventing excessive irradiation of the abducent nerve (Fig. 7). Within 2 weeks after the treatment, the pre-existing diplopia resolved completely. However, 1 year later, the patient experienced sudden clinical deterioration accompanied by an increase in her plasma cortisol level, and MRI once again demonstrated tumor regrowth with invasion of the left superior petrosal sinus. The third GKS was performed with delivery of a 20 Gy marginal dose at the 50% isodose line (Fig. 8). At 1-year follow-up after the last treatment, the clinical condition of the patient was stable and her endocrinological function had significantly improved.

Alternative Treatment Options

Invasion of the CS is encountered in 7–42% of PA, and its presence is frequently considered a sign that the tumor is biologically aggressive [2, 22, 39–42]. Effective management of such lesions is rather challenging. Contemporary advances in neuroimaging and neuroanesthesiology; availability of computer-aided devices for preoperative planning and simulation of neurosurgical procedures; and possible use of comprehensive intraoperative neurophysiological monitoring, complex surgical approaches, and thorough microsurgical and neuroendoscopic techniques allow aggressive resection of virtually any skull base tumor [2–4]. However, even in modern series, GTR of a PA with CS invasion corresponding to Knosp grades 3–4 is possible in roughly 60–70% of cases [3, 22]. Postoperative morbidity—particularly related to at least temporary dysfunction of the cranial

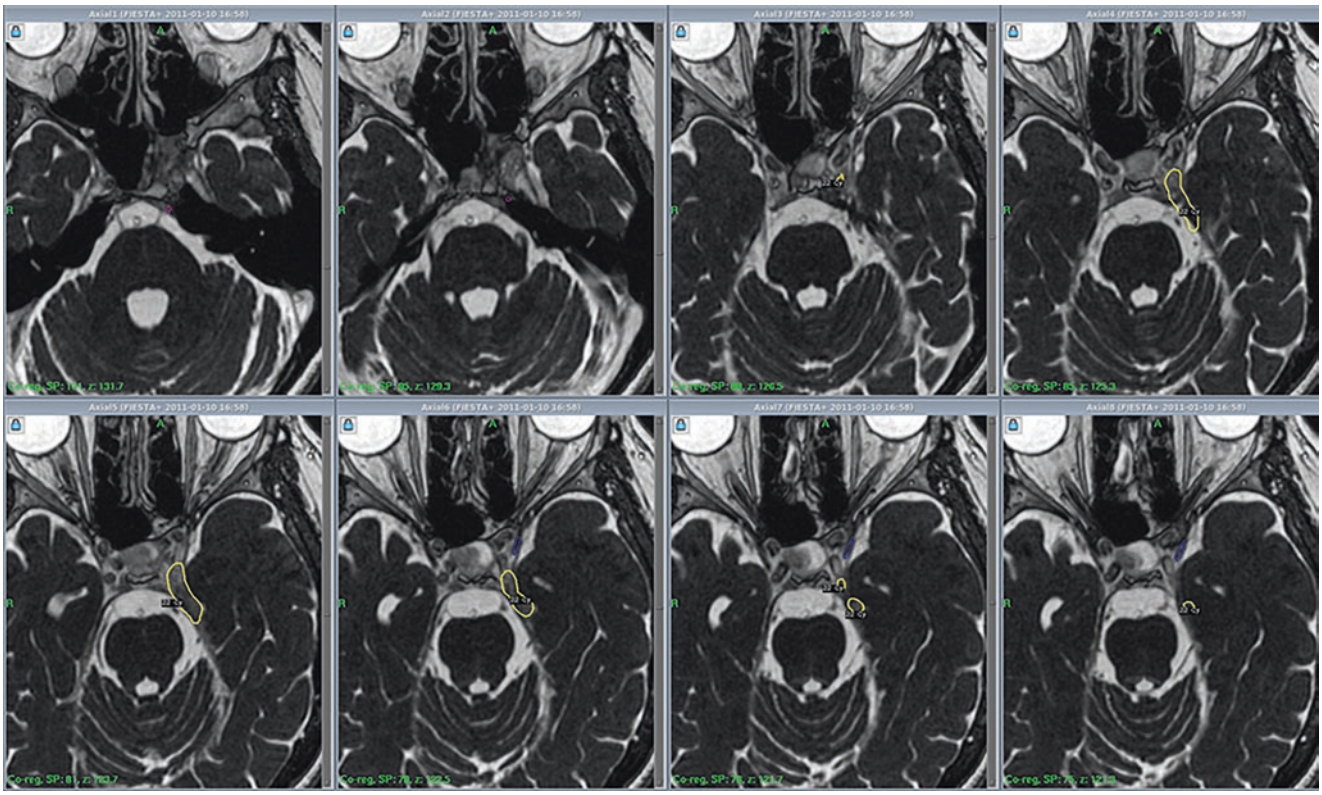

Fig. 8 Treatment plan based on postcontrast three-dimensional (3D) constructive interference in steady state (CISS) images at the time of the third Gamma Knife radiosurgery for regrowth of an adrenocorticotropic hormone (ACTH)–secreting pituitary adenoma with invasion of the left superior petrosal sinus, manifesting with a sudden increase in the plasma cortisol level. The tumor was covered with a 20 Gy marginal dose delivered at the 50% isodose line (*yellow circle*)

nerves—is not negligible, and its incidence varies from 27% to 50% [3, 4], which is highly undesirable considering the benign nature of these tumors.

Pure observation after incomplete resection of a nonfunctioning PA results in tumor regrowth in 50–60% of patients within 10 years of surgery [43, 44], whereas in cases of hormone-secreting tumors, it does not allow normalization of endocrinological function. While dopamine agonist therapy has shown good effectiveness in cases of prolactinomas, the presence of CS invasion may be associated with their greater resistance to medical treatment [45]. Finally, FRT may provide good tumor growth control but is associated with relatively high risks of various long-term complications, including hypopituitarism, optic neuropathy, cranial nerve palsy, ICA stenosis, stroke, neurocognitive abnormalities, radiation-induced cerebral injury, and development of secondary neoplasms. Additionally, normalization of pituitary hormone hypersecretion after FRT is very slow [1, 9, 11].

Therefore, in comparison with other treatment options, SRS—in particular, GKS—seemingly provides the most beneficial results in patients with a residual intracavernous PA, although direct prospective comparisons of the different treatment modalities in such cases are generally not available. It should be emphasized that oncological and endocrinological outcomes after SRS, including tumor growth control and development of delayed hypopituitarism, are directly related to the lesion volume before irradiation; thus, even if GTR cannot be accomplished during surgery, maximal subtotal safe removal of the neoplasm is highly desirable.

Remaining Questions and Future Perspectives

One of the most important questions after incomplete resection of a PA is when to perform postoperative SRS. Early treatment is clearly indicated in patients with increased hormone secretion to achieve improvement or normalization of endocrinological function. However, in nonfunctioning PA, clinical decision-making is more complex. Nevertheless, a retrospective analysis from the University of Virginia demonstrated that delayed GKS in such cases may be associated with significantly greater risks of lesion regrowth during the observation period, a worse tumor response to irradiation, and postradiosurgery progression of PA and endocrinopathy [43]. A subsequent retrospective multicenter matched-cohort study also showed that delayed treatment may result in a worse tumor response and a greater risk of postradiosurgery

progression [44]. These data indicate that early administration of GKS (i.e., within 6 months after incomplete resection of a nonfunctioning PA) may carry greater benefits for the patient.

For lesions whose size or location preclude administration of single-session SRS, it remains unclear whether multisession SRS with delivery of 2–5 fractions and/or hypofractionated stereotactic radiotherapy (SRT) may be substituted for traditional FRT and result in comparable or better tumor control rates, endocrinological outcomes, and safety profiles. This should be investigated in further prospective studies, preferably performed on a multi-institutional basis with involvement of sufficient numbers of patients.

Is Selective Treatment Reasonable?

Another question is whether highly selective treatment planning, as has been consistently applied in our patients, is really necessary or even reasonable. It is evident that excessive irradiation of the anterior optic pathways should be avoided. The recommended safe maximal doses for prevention of radiation-induced optic neuropathy range from 8 to 12 Gy (10 Gy in our practice) and may be lowered further in previously irradiated cases or if there is significant preexisting deterioration of visual function [1, 13, 27, 31]. In contrast, much higher radiation doses may be tolerated by other adjacent cranial nerves, whose functional alteration (which is usually transient) after SRS of CS lesions has been noted in 0–13% of cases, although the risk of injury may be increased after repeat irradiation [1, 6, 9, 12, 13, 27, 31]. In any case, the rate of this complication in the majority of previous reports was still higher than the incidence in our patients (2%), albeit reliable comparison of various series is quite difficult because of differences in the equipment used, the doses delivered, and the pathologies treated. In addition, possible long-term effects of high-dose irradiation of the intracavernous cranial nerves remain unknown.

An attempt at highly selective radiation delivery can also result in an insufficient rate of endocrinological normalization after GKS for hormone-secreting tumors. In our series, this treatment effect occurred in 18 out of 46 cases (39%), a rate somewhat lower than those mentioned in other reports (which have described mean rates of 51.1%, 44.7%, and 34.7% in ACTH-secreting, GH-secreting, and prolactin-secreting PA, respectively [1]). Furthermore, critical interpretation of the presented illustrative case 3 may suggest that highly selective irradiation might result in early tumor regrowth, as was observed twice in that young woman.

On the other hand, none of our patients has experienced new postradiosurgery endocrinopathy, whose mean incidence after SRS for different types of PA has varied from 8.8% to 24.3%, with even higher rates (of up to 40% and 70% in nonfunctioning and hormone-secreting tumors, respectively) being reported in some studies [1]. The somatotropic axis is considered the most vulnerable, followed by the gonadotropic, the adrenocorticotropic, and the thyrotropic axes [37]. The main factors affecting the rate of hypopituitarism after SRS include the patient's age, the modalities and timing of previous treatments, the pituitary function status before irradiation, the radiation dose delivered to the pituitary stalk and gland (but not to the hypothalamus), and the rigorousness and length of endocrinological follow-up [1, 32, 35, 37]. Vladyka et al. [37] identified cutoff values of 15 Gy for the mean dose delivered to the pituitary gland for preservation of gonadotropic and thyrotropic function, and 18 Gy for preservation of adrenocorticotropic function. In addition, in their study, worsening of pituitary function after GKS was significantly dependent on the maximal dose delivered to the pituitary stalk, and this was encountered more frequently in cases with suboptimal lesion visualization on imaging and nonselective irradiation [37]. Of note, in the series that included only intracavernous PA cases, the reported rate of new hypopituitarism after SRS was somewhat lower (0–4%) [7–9, 12, 28–30], which may have been explained by the more lateral location of the target at a distance from critical neuroendocrine structures.

As is the case in open microneurosurgical procedures, during radiosurgical treatment planning and dosimetry, it is always necessary to keep a balance between achievement of the greatest possible benefits and maximal reduction of the accompanying risks. SRS is a minimally invasive and easily repeatable procedure, so it can be performed again if needed. At the same time, treatment of radiation-induced complications (e.g., cranial neuropathy or a new hormone deficit), especially permanent ones, may be difficult, and they may carry lifelong consequences for a patient; thus, every possible effort should preferably be put into their prevention. In our opinion, this justifies highly conformal and selective treatment planning with avoidance of excessive dose delivery to functionally important neurovascular structures in proximity to the target, as we advocate consistently not only for GKS but also for other types of stereotactic irradiation (e.g., for heavy ion therapy). In general, such a radiosurgical treatment strategy follows the principles of microneurosurgery (i.e., attacking the target lesion with maximal preservation of all adjacent normal structures) [16].

Further increases in the effectiveness and safety of SRS are closely related to advances in neuroimaging. Novel MRI sequences may allow much greater image resolution. For example, Tong et al. [46] demonstrated that a postcontrast 3D sampling perfection with application-optimized contrasts by using different flip angle evolutions (SPACE) sequence on 3T MRI is more effective than 3D CISS for identification of CS invasion by PA. Additional options are provided by metabolic imaging. Koulouri et al. [47] reported good efficacy of ^{11}C-methionine positron emission tomography (PET)

coregistered with MRI for identification of a residual GH-secreting PA after previous therapy and differentiation of treatment-induced changes. These promising results open new perspectives, and testing of such imaging techniques during radiosurgical treatment planning is highly warranted.

Conclusion

Contemporary GKS based on advanced imaging and computer-aided technology has proved its high effectiveness and safety in cases of residual or recurrent PA invading the CS, and allows for highly conformal and selective radiation delivery to the target with preservation of adjacent functionally important neurovascular structures. In the experience of such treatment gained at Tokyo Women's Medical University, with a minimum follow-up period of 5 years (mean 76 months, range 60–118 months), the tumor control rate has reached 97% and significant volume reduction (≥50%) has been seen in 24% of lesions. In patients with a hormone-secreting PA, normalization (39%) or improvement (48%) of endocrinological function has been noted. Importantly, these treatment effects have been sufficiently durable. Complications have been extremely rare and limited to transient cranial nerve palsy in 2% of cases. Notably, no patient in our series has had a new pituitary hormone deficit after irradiation. Thus, subtotal resection followed by GKS may be considered a valuable alternative to aggressive surgery for a PA invading the CS.

Conflict of Interest The authors have no conflict of interest concerning the reported materials or methods.

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Stereotactic Radiosurgery for Pituitary Carcinoma

Gautam U. Mehta and Ian E. McCutcheon

Abstract A pituitary carcinoma (PC) is a rare neoplasm, accounting for only 0.2% of pituitary tumors, and is defined by the presence of noncontiguous metastatic disease. Its management requires a multimodal approach including surgery, irradiation, and medical therapy. Stereotactic radiosurgery (SRS) by means of the Gamma Knife or CyberKnife may be considered potentially useful in such cases. It has mainly been applied for localized metastases and symptomatic lesions, but it may also be effective in control of aggressive tumor growth at the primary site after sufficient surgical debulking of the lesion. Given the infrequency of PC and their heterogeneous nature with regard to the histopathological type, local extension, and location of metastases, large clinical series have not been compiled to date. While, in such cases, SRS is certainly not curative and does not prevent disease progression, it is quite reasonable to incorporate this treatment option into a multimodal management strategy and apply it judiciously at the treating clinician's discretion on a case-by-case basis.

Keywords CyberKnife radiosurgery · Gamma Knife radiosurgery · Metastatic disease · Pituitary adenoma · Pituitary carcinoma · Stereotactic radiotherapy

Introduction

While the majority of pituitary adenomas (PA) are benign and slow-growing lesions, they frequently demonstrate somewhat invasive growth [1, 2]. Additionally, certain histological subtypes of these tumors (e.g., sparsely granulated somatotroph adenomas, silent corticotroph adenomas, and Crooke cell adenomas) are more prone to invasion and to difficulty in achieving persistent remission [3]. However, despite frequent locally invasive or clinically aggressive behavior, only 0.2% of PA eventually metastasize [4]. The presence of noncontiguous metastasis (but not specific histological features) defines a pituitary carcinoma (PC).

General Characteristics of Pituitary Carcinomas

PC often show acquisition of mutations in *TP53* and significantly increased MIB-1 immunolabeling for Ki-67 protein [2, 5]. However, in some cases, the MIB-1 index is low and overlaps with the expected values seen in benign PA (i.e., <3%) [2, 6]. Whereas only half of PA are hormone-secreting, nearly 90% of PC have detectable hormone production [7–10], and the majority of them secrete either prolactin or adrenocorticotropic hormone (ACTH) [8].

Although there is typically a delay (mean 6.5 years) from diagnosis of a PA to development of metastatic disease, such tumors are rapidly progressive once they show noncontiguous spread. The overall survival rate of patients at 1 year after diagnosis of the first metastasis is only 33% [9]. While initial management of PA (other than prolactinomas) is usually microsurgical tumor resection, PC require a multimodal treatment strategy including surgery, irradiation, and medical therapy. Nevertheless, because of the rarity of these tumors, neither treatment outcomes nor management paradigms—specifically, in regard to fractionated radiotherapy (FRT), stereotactic radiosurgery (SRS), chemotherapy, or their combination—have been fully defined.

G. U. Mehta · I. E. McCutcheon (✉)
Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: imccutch@mdanderson.org

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*, Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_5,

Radiotherapy and Stereotactic Radiosurgery for Pituitary Adenomas

Irradiation of the sellar and parasellar area has been used to treat PA since the early 1900s and constitutes an important adjunct to their management [7, 11, 12]. Nowadays, treatment may be done either as conventional FRT or as SRS, and both of these techniques have increasingly become a standard second-line therapeutic option for several types of PA, including ACTH-secreting tumors (causing Cushing's disease), growth hormone (GH)–secreting tumors (resulting in acromegaly or gigantism), and carefully selected nonfunctioning pituitary tumors [7, 13].

Therapeutic irradiation over multiple fractions offers the benefit of reduced cranial nerve toxicity, particularly for lesions adjacent to the optic apparatus [14]. Conversely, SRS allows highly selective and conformal high-dose single-session treatment—in particular, resulting in a shorter time to remission in cases of hormone-secreting PA [15–17]. This modality is based on precise stereotactic localization of a radiographically defined target and focusing of converging beams of irradiation on it with a steep dose falloff at the margin of the treatment volume. The most common technological devices used for SRS of PA are the Leksell Gamma Knife (Elekta AB; Stockholm, Sweden), which is typically a frame-based technique, and the CyberKnife (Accuray; Sunnyvale, CA, USA) which allows for frameless treatment, thus facilitating administration of multisession SRS and hypofractionated stereotactic radiotherapy (SRT). Usually, the prescribed marginal dose in cases of nonfunctioning PA ranges from 12 to 20 Gy, but it is greater (from 18 to >25 Gy) in hormone-secreting tumors, since the goals of SRS in such cases include both lesion growth control and endocrine remission [18].

Impact of Radiotherapy on Tumorigenesis of Pituitary Carcinomas

Many patients who eventually develop a PC initially present with a locally invasive tumor and multiple recurrences at the primary site. Because, in such cases, FRT is often part of combined treatment, it has been suggested that irradiation itself may have an impact on tumorigenesis of PC. Lall et al. [19] found that in 45 out of 46 reported cases of such tumors (98%), sellar/parasellar irradiation was given before appearance of metastases. However, a "post hoc ergo propter hoc" fallacy must be avoided; it is evident that FRT is more likely to be recommended for locally aggressive neoplasms [20]. Of note, other authors have not found the aforementioned association. In an earlier review, Mountcastle et al. [21] noted that fewer than half of the patients with PC (18 out of 38) had previously received sellar irradiation. In concordance, analysis of the Surveillance, Epidemiology, and End Results (SEER) database revealed seven cases of PC, but only in one of them was FRT given beforehand [22].

Radiotherapy for Pituitary Carcinomas

Although conventional FRT has been utilized for scattered cases of PC for several decades, few related data have been reported. For example, on the basis of a clinicopathological study, Pernicone et al. [9] presented one of the largest series of such tumors and briefly noted that 10 out of 15 patients received radiotherapy for treatment of metastases, but they did not provide either treatment details or outcome data. Given the infrequency of PC and their heterogeneous nature (in particular, with regard to the histopathological type, local extension, and location of metastases), large clinical series have not been compiled to date. Nevertheless, analysis of the several case reports that have described application of FRT for pituitary tumors with metastatic spread and the results of such treatment allows some understanding of the radiobiology of these rare neoplasms.

Efficacy of Combined Treatment

FRT has not typically been used as a stand-alone treatment for distant metastases or aggressive local extension of PC (Table 1). Two reports have described its postoperative administration after surgical tumor debulking, which resulted in local control for 3 years in one patient [6] and for 5 years in another [25]. Alternatively, FRT has been applied concurrently with systemic anticancer drugs, such as cisplatin, temozolomide (TMZ), and the mammalian target of rapamycin (mTOR) inhibitor everolimus [6, 23, 24, 26]. In one patient, chemotherapy with cisplatin combined with spinal irradiation resulted in tumor control for 2 years and a reduction in radicular pain [23]. In two other comparable cases of thoracic vertebral body and pelvis/sacrum metastases treated by a combination of everolimus and FRT, short follow-up periods precluded analysis of treatment effectiveness, but at least one patient experienced symptomatic improvement [26]. In two reports, irradiation was administered concurrently with TMZ and provided effective medium-term tumor growth control (for 1–1.5 years) [6, 24]. Of note, chemotherapy with TMZ, an alkylating agent with good penetration through the blood–brain barrier, may result in an initial response of the PC, but these neoplasms still progress eventually [27–29]. Finally, one patient, in

Table 1 Previously reported cases of fractionated radiotherapy (FRT) for pituitary carcinoma

Study	Characteristics of pituitary tumor	Site of treated tumor	Treatment modality	Total dose (Gy)	Number of fractions	Concurrent therapy	Outcome	Adverse radiation effects
Beauchesne et al. (1995) [23]	Gonadotropin-secreting	Diffuse spinal spread	FRT	30	15	Cisplatin	Tumor control for 2 years, improved sciatica	None
Morokuma et al. (2012) [24]	Nonfunctioning	Diffuse meningeal spread	WBRT	30	ND	TMZ	Tumor regression for 1.5 years	Hair loss, mild bone marrow suppression
Arnold et al. (2012) [25]	ACTH-secreting	L2–L3 intradural extramedullary tumor	Postoperative local-field FRT	ND	ND	None	Local recurrence 5 years later	None
Kamiya-Matsuoka et al. (2016) [6]	Nonfunctioning (case 1)	Cervical lymph nodes, local extension into infratemporal fossa	FRT	54	28	TMZ	Tumor control for 1 year	None
	ACTH-secreting (case 2, lesion 1)	Local extension into orbit	Postoperative local-field FRT	45	25	None	No local recurrence within 3 years	None
	ACTH-secreting (case 2, lesion 2)	Portacaval lymph node	Hypofractionated SRT	70	10	TMZ	Tumor control for 2.5 years	None
Donovan et al. (2016) [26]	ACTH-secreting (lesion 1)	Pelvis/sacrum	FRT	30	ND	Everolimus	Tumor control for 4 months	None
	ACTH-secreting (lesion 2)	T9–T10 vertebral bodies	FRT	30	ND	Everolimus	Pain improvement, otherwise ND	None

ND no data, *SRT* stereotactic radiotherapy, *TMZ* temozolomide, *WBRT* whole-brain radiotherapy

addition to postoperative local-field FRT for a tumor extending into the orbit, received hypofractionated SRT (70 Gy in ten fractions) concurrently with TMZ for portacaval lymph node metastasis, which resulted in its control for 2.5 years [6]. Overall, these data suggest that while the results of FRT alone for PC are generally unknown, its combination with chemotherapy may contribute to effective local tumor control, at least during medium-term follow-up. Importantly, the treatment has usually been well tolerated, and minimal adverse radiation effects have been noted.

Stereotactic Radiosurgery for Pituitary Carcinomas

In our own experience, SRS is used most commonly to treat focal metastases of PC defined on magnetic resonance imaging (MRI), and is applied less often for sellar/parasellar tumors themselves, since prior surgery and proximity to the optic nerves and chiasm impose more ambiguous radiographic margins of the target lesion and limit radiation dosimetry. Moreover, as a result of previous FRT, adjacent critical neurovascular structures' tolerance of additional high-dose irradiation may be significantly decreased.

We were able to identify only two reports (Table 2) on SRS for metastasizing pituitary tumors—that is, for true PC. In both cases, the neoplasm initially presented as a prolactinoma. Phillips et al. [30] described a patient who had aggressive local growth of the tumor at the primary site and presented with a dural-based metastasis in the right temporal area 22 months after the initial manifestation of the disease. Gamma Knife surgery (GKS) targeted the sellar/parasellar lesion and resulted in its shrinkage, but the untreated temporal mass continued to grow. Despite salvage chemotherapy with TMZ, the patient died 15 months after irradiation [30]. Park et al. [31] reported a PC metastasizing into the fourth ventricle 7 years after its initial presentation and management. The tumor was subtotally resected, and the residual mass was treated with GKS (with a marginal dose of 16 Gy at the 50% isodose line), which led to its control during 3 years of follow-up [31]. The treatment results described in these reports corroborate our own experience in similar cases well (Figs. 1 and 2).

Table 2 Previously reported cases of stereotactic radiosurgery for pituitary carcinoma

Study	Characteristics of pituitary tumor	Site of treated tumor	Treatment modality	Prescription dose (Gy)	Number of sessions	Concurrent therapy	Outcome	Adverse radiation effects
Phillips et al. (2012) [30]	Prolactinoma	Sella, right cavernous sinus	GKS	ND	1	None	Regression of treated tumor, growth of untreated lesions	None
Park et al. (2014) [31]	Prolactinoma	Fourth ventricle	Postoperative GKS for a residual tumor	16	1	None	Tumor control for 3 years	None

GKS Gamma Knife surgery, *ND* no data

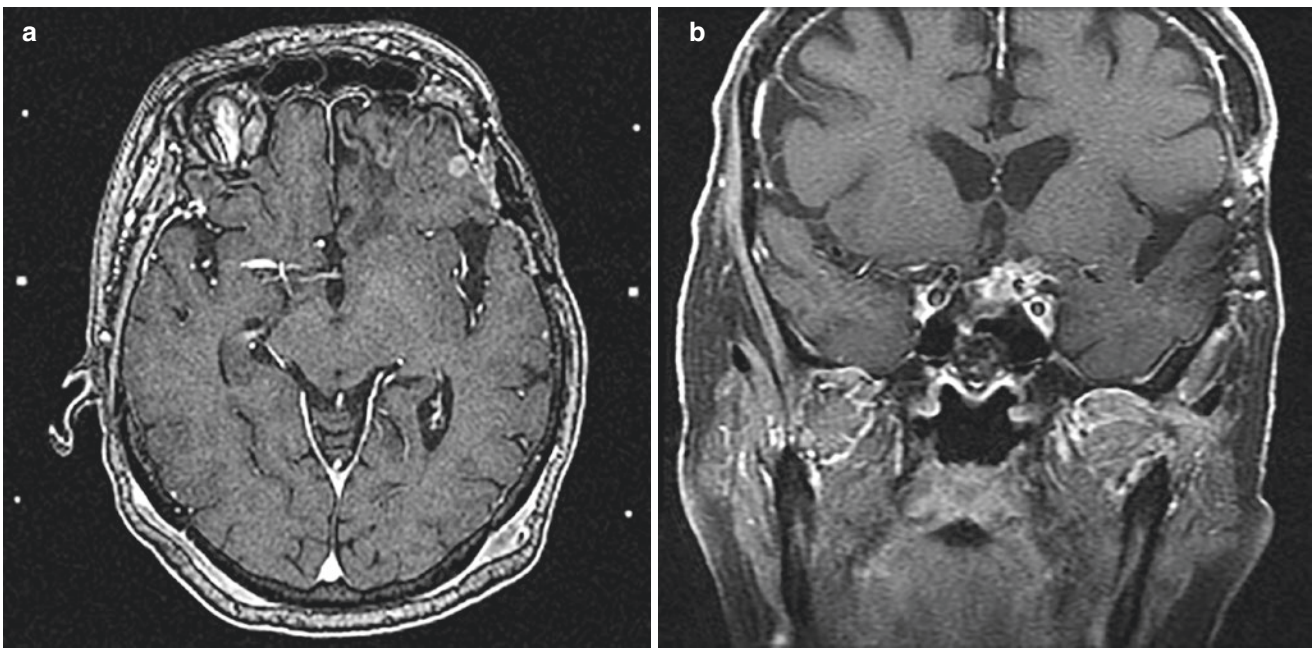

Fig. 1 An 81-year-old woman with a dural-based metastasis noted 7 years after presentation with a prolactin-secreting pituitary macroadenoma. Therapy with a dopamine agonist at the time of initial diagnosis proved ineffective in controlling tumor growth; thus, the intra- and suprasellar portions of the lesion were removed via the transsphenoidal approach. Subsequently, the patient underwent two left-sided craniotomies for resection of the relapsing neoplasm and received adjuvant fractionated radiotherapy for a residual mass in the left cavernous sinus. Three months after her second craniotomy, tumor metastasis was disclosed. Magnetic resonance imaging (MRI) demonstrated a nodular contrast-enhancing lesion adjacent to the left frontobasal dura (**a**, *arrow*), which had not been visible during the prior imaging examination. At that time, the patient's serum prolactin level was 727 ng/mL, and MRI showed residual fibrosis and an invasive tumor in the left side of the sella and in the superior portion of the adjacent cavernous sinus (**b**). Growth of the metastatic tumor was well controlled by Gamma Knife radiosurgery, with a marginal dose of 20 Gy delivered at the 50% isodose line. However, 7 months later, multiple new dural-based metastases appeared, shortly before the death of the patient from pneumonia

Because of the paucity of reports on PC treated with SRS after the appearance of metastatic spread, analysis of the results of such treatment in locally aggressive pituitary tumors just prior to development of metastases may give some insight into the radiobiological characteristics of these lesions. Sufficient surgical debulking of the neoplasm via the transsphenoidal or transcranial approach before irradiation may be an important prerequisite for attainment of an optimal outcome, since it allows reduction of the target volume and decompression of adjacent neurovascular structures—in particular, the anterior visual pathways. Ono et al. [32] described a patient complaining of double vision caused by an ACTH-secreting PA, who underwent transsphenoidal removal followed by GKS (with a marginal dose of 25 Gy) for a residual mass in the right cavernous sinus. The treatment resulted in resolution of diplopia at 3 months after irradiation, but 8 months later, the tumor demonstrated extensive regrowth into the temporal bone, resulting in lower cranial nerve palsy. The patient underwent repeat GKS (with a marginal dose of 15 Gy), which, again, resulted in resolution of symptoms. However, 3 months later, a new tumor recurrence was confirmed in the right cavernous sinus; thus, GKS (with

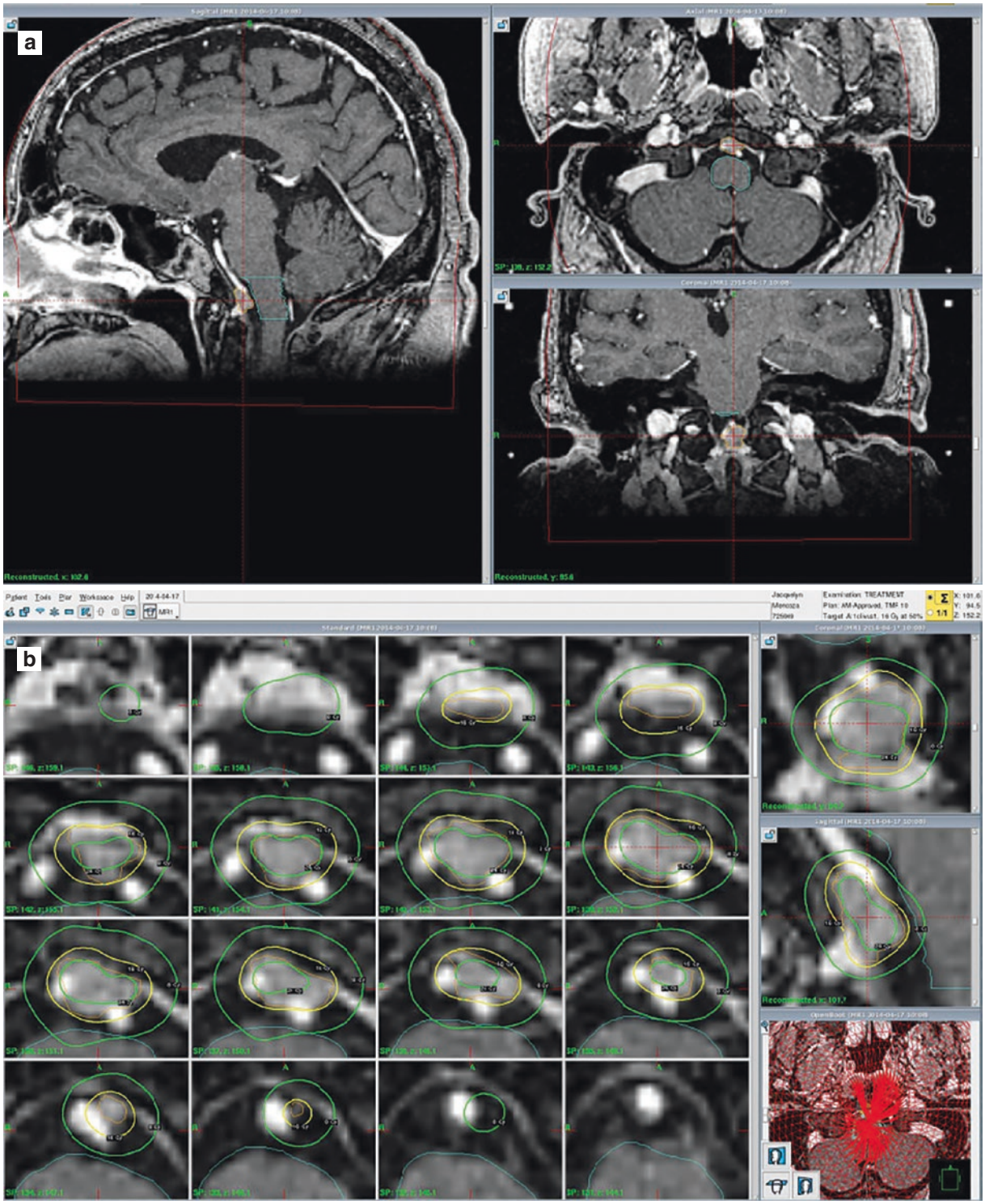

Fig. 2 A 23-year-old woman with metastasis to the lower clivus noted 8 years after presentation with clinical hypercortisolism caused by an adrenocorticotropic hormone (ACTH)–secreting pituitary macroadenoma with suprasellar extension and invasion of the right cavernous sinus. The patient underwent (in succession) transsphenoidal tumor debulking, craniotomy for further tumor debulking, fractionated radiotherapy for the residual lesion (total dose 48.8 Gy), a second craniotomy, and chemotherapy, first with capecitabine and temozolomide, and then with carboplatin and 5-fluorouracil (which yielded tumor shrinkage and lowered, but did not normalize, her plasma ACTH level). As the clival metastasis (**a**) demonstrated resistance to chemotherapy and continued to grow, at 2 years after its initial discovery, it was treated with Gamma Knife radiosurgery, with a marginal dose of 16 Gy delivered at the 50% isodose line (**b**; the isodose lines corresponding to 24, 16, and 8 Gy are shown; note the minimal irradiation of the adjacent brainstem). After treatment, the lesion demonstrated a prominent volume reduction and a sustained and durable response. Four years later, the patient remained alive with radiographically stable disease and partially controlled hypercortisolism

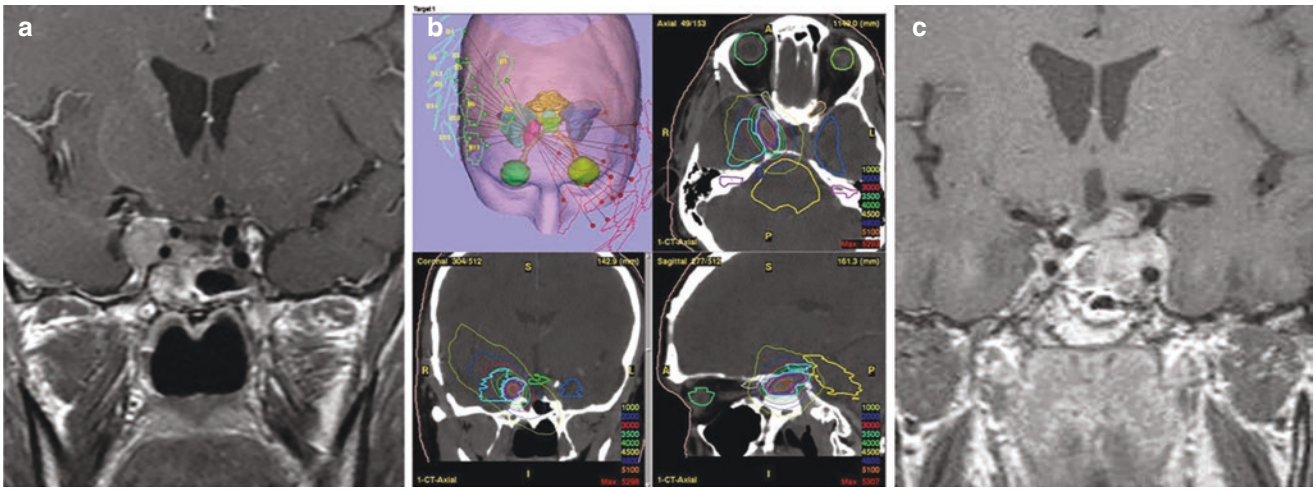

Fig. 3 Fractionated stereotactic radiotherapy (SRT) of a recurrent pituitary carcinoma, resulting in local tumor control. A 37-year-old man presented with diplopia caused by a nonfunctioning pituitary macroadenoma and underwent subtotal lesion resection via the transsphenoidal approach and subsequent Gamma Knife radiosurgery for a residual mass at a different institution. The tumor responded to treatment but demonstrated regrowth 3 years later. Four years after the initial presentation, repeat transsphenoidal surgery was performed at our hospital, but the neoplasm relapsed within 1 year, which required its additional removal via right-sided craniotomy. With histopathology revealing an MIB-1 index of 7.1% and 3 mitoses per 10 high-power fields, further rapid progression within and adjacent to the right cavernous sinus was noted 6 months later (**a**). Because of the proximity of the optic apparatus and previous radiosurgery, fractionated SRT using the CyberKnife, with a total dose of 45 Gy delivered in 25 fractions, was performed (**b**). Although the right cavernous sinus lesion eventually regressed, out-of-field tumor progression in the sella and left cavernous sinus was noted (**c**). This recurrence coincided with the onset of multiple metastases in the interpeduncular fossa, the posterior fossa dura, the cerebellum, and the intradural extramedullary space at the level of C2. The patient underwent repeat craniotomy for decompression of the anterior visual pathways and was started on temozolomide; however, it had limited efficacy. He died from slow but unrelenting disease progression with extensive metastatic spread of the tumor both within the neuroaxis and to systemic sites. In total, he survived for 13 years after the initial diagnosis and 5 years after the first appearance of metastases. (Reproduced in part from McCutcheon [33])

a marginal dose of 15 Gy) was performed for the third time and led to resolution of the presenting diplopia within 1 month. Unfortunately, 9 months later, the patient was diagnosed with multiple liver metastases [32]. A very similar case from our own practice has been reported in part previously (Fig. 3) [33].

Taken together, the findings from these cases of PC treated with SRS after and before metastatic spread suggest that this treatment modality may be effective for controlling both noncontiguous tumors and aggressive growth of the neoplasm at the primary site. Although stereotactic irradiation is certainly not curative and does not prevent remote disease progression, it may be useful for management of localized disease and symptomatic lesions. Moreover, as with PA in general, this treatment modality is likely to be specifically effective in a particular subset of patients, but, obviously, it cannot be defined without analysis of larger series, which are currently not available. Therefore, further studies performed on a multi-institutional basis, and preferably in a prospective fashion, are required for clarification of the indications for SRS, its efficacy, and the durability of the tumor response in patients with PC.

Conclusion

Few systematic studies exist on the use of SRS in cases of PC. As the histology and location of tumors, the functional status of patients, and the total disease burden have varied widely across the reported cases, meaningful clinical conclusions cannot be reached. Nevertheless, the occasionally reported results suggest that this modality may have a role in initial and salvage treatment of patients with such neoplasms. While no class I–III evidence on the use of SRS for PC currently exists, it is quite reasonable to incorporate this treatment option into a multimodal management strategy and apply it judiciously at the treating clinician's discretion on a case-by-case basis.

Conflict of Interest The authors have no conflict of interest concerning the reported materials or methods.

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Evidence-Based Recommendations for Seizure Prophylaxis in Patients with Brain Metastases Undergoing Stereotactic Radiosurgery

Arvin R. Wali, Robert C. Rennert, Sonya G. Wang, and Clark C. Chen

Abstract Symptomatic epilepsy is frequently encountered in patients with brain metastases (BM), affecting up to 25% of them. However, it generally remains unknown whether the risk of seizures in such cases is affected by stereotactic radiosurgery (SRS), which involves highly conformal delivery of high-dose irradiation to the tumor with a minimal effect on adjacent brain tissue. Thus, the role of prophylactic administration of antiepileptic drugs (AED) after SRS remains controversial. A comprehensive review and analysis of the available literature reveals that according to prospective studies, the incidence of seizures after SRS for BM varies from 8% to 22%, and there is no evidence that SRS increases the incidence of symptomatic epilepsy. Therefore, routine prophylactic administration of AED prior to, during, or after SRS in the absence of a seizure history is not recommended. Nevertheless, short-course administration of an AED may be judiciously considered (on the basis of class III evidence) for selected high-risk individuals.

Keywords Antiepileptic drugs · Fractionated radiotherapy Intracranial metastases · Prophylactic antiepileptic therapy Seizures · Stereotactic radiosurgery · Symptomatic epilepsy

Sonya G. Wang and Clark C. Chen contributed equally as senior authors of the present study.

A. R. Wali · R. C. Rennert
Department of Neurosurgery, University of California San Diego (UCSD), La Jolla, CA, USA

S. G. Wang
Department of Neurology, University of Minnesota Medical School, Minneapolis, MN, USA

C. C. Chen (✉)
Department of Neurosurgery, University of Minnesota Medical School, Minneapolis, MN, USA
e-mail: ccchen@umn.edu

Introduction

Symptomatic epilepsy is one of the devastating consequences associated with brain cancers. It affects up to 25% of all patients with brain metastases (BM), is frequently accompanied by depression and anxiety, and adversely impacts the quality of life (QOL) of afflicted individuals in more ways than the seizure-induced injuries [1–3]. The use of antiepileptic drugs (AED) is generally effective in seizure suppression, but all AED are accompanied by potential side effects, which may compromise QOL [4]. Therefore, while patients with BM suffering from epilepsy are typically given AED, prophylactic therapy in the absence of a seizure history is generally not recommended [5].

Since the blood–brain barrier prevents penetration of most chemotherapy agents into the central nervous system (CNS), radiation treatment remains a mainstay option for management of BM [6, 7]. Tumor resection may be performed in those patients who are deemed suitable surgical candidates [8]. Stereotactic radiosurgery (SRS) allows delivery of high radiation doses in a highly conformal manner attained by convergence of multiple, nonparallel beams of irradiation on the target [9, 10]. This treatment modality has demonstrated high effectiveness in the treatment of BM.

Whether SRS exacerbates epilepsy in patients with BM remains poorly understood. On one hand, it is well recognized that irradiation of the cerebrum is associated with an increased risk of seizures [11], but, the probability of this side effect may be negligible after SRS, since highly conformal radiation delivery limits adjacent brain volume exposure [9, 10].

The present analysis was based on a comprehensive literature search with an objective of identifying existing reports on seizure risk following SRS for BM. The goal of our study is to characterize the efficacy and current pattern of clinical practice in terms of prophylactic AED during SRS of BM.

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*,
Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_6,

Materials and Methods

The PubMed database was searched for references published from January 1, 1990, through June 25, 2016, using the terms *seizure*, *stereotactic radiosurgery*, *intracranial metastasis*, and *Gamma Knife* as keywords. This search revealed 550 relevant articles. To identify pertinent information, we required a report presenting original research (i.e., not a review or editorial), based on a study involving human subjects, and published in the English language. The articles that fulfilled these selection criteria were further reviewed by two authors (ARW and RCR) to identify studies that (1) prospectively followed up patients with BM after SRS to establish the risk of seizures, (2) provided insights in terms of the efficacy of prophylactic AED use in such cases, and (3) established patterns of clinical practice in terms of prophylactic AED use.

Results

Overall, we identified four articles [12–15] that addressed the risk of seizures in patients with BM after SRS, one article [16] that highlighted the efficacy of prophylactic AED use in such cases, and one article [17] that characterized patterns of clinical practice in terms of prophylactic AED use.

Risk of Seizures in Patients with Brain Metastases After Radiosurgery

While seizure frequency has been a reported outcome in many published studies on BM, it is difficult to tease out whether epilepsy in these cases manifested prior to or after SRS. To address this issue, only prospective studies of new onset seizures after SRS were included and evaluated in our analysis. They are summarized in Table 1.

Chitapanarux et al. [12] prospectively followed up 41 adult patients (median age 55 years, range 30–75 years) with 1–4 BM, who underwent SRS (with a median marginal dose of 18 Gy delivered at the 90% isodose line) for a total of 77 tumors. An exclusion criterion was a tumor origin of either small cell lung cancer or lymphoma. The median Karnofsky Performance Scale (KPS) score before treatment was 90 (range 60–100), and the majority of patients (54%) presented with one BM. Primary site cancer control and absence of extracranial metastases by the time of treatment were noted in 51% and 35% of cases, respectively. Non–small cell lung carcinoma (NSCLC) was the most common source of BM (in 37% of cases), followed by renal cell carcinoma (RCC) (in 32% of cases), melanoma (in 16% of cases), and breast cancer (in 10% of cases). Within a median follow-up period of 7 months (range 1.5–31 months) after SRS, a total of 9 patients (22%) had seizures [12].

Lutterbach et al. [13] prospectively followed up 101 adult patients (mean age 59 years, range 29–80 years) with 1–3 BM who underwent SRS (with a median marginal dose of 18 Gy delivered at the 80% isodose line) for a total of 155 tumors. The exclusion criteria included a tumor diameter >3 cm, a KPS score <50, and prior radiation treatment. In 81% of cases, the KPS score before SRS was ≥70, and the majority of patients (55%) presented with one BM. Primary site cancer control and absence of extracranial metastases by the time of treatment were noted in 67% and 39% of cases, respectively. Lung cancer was the most common source of BM (in 27% of cases), followed by breast cancer (in 20% of cases), RCC (in 15% of cases), melanoma (in 12% of cases), gastrointestinal cancer (in 12% of cases), and urogenital cancers (in 6% of cases). During a median follow-up period of 7.6 months after SRS, a total of nine patients (9%) had seizures or transient worsening of pre-existing neurological symptoms, which subsequently resolved [13].

Williams et al. [15] prospectively followed up 273 patients (median age 57 years, range 12–93 years) with 1–2 BM who underwent SRS (with a median marginal dose of 18 Gy delivered at the 50% isodose line) for a total of 316 tumors. An exclusion criterion was prior radiation treatment. The median KPS score before SRS was 90 (range 40–100), and the majority of patients (84%) presented with one BM. The median volume of the intracranial tumors was 1.26 cc (range 0.01–22 cc). No information was provided with regard to primary site cancer control and the presence of extracranial metastases. Lung cancer was the most common source of BM (in 36% of cases), followed by melanoma (in 25% of cases), RCC (in 17% of cases), breast cancer (in 13% of cases), and sarcoma (in 2% of cases). The median length of follow-up after SRS was 19.9 months (range 1.0–90.8 months). The authors noted that by the 3-month follow-up, a total of 41 patients (15%) had experienced seizures. The incidence was higher (20% versus 11%, $P < 0.001$) in cases of tumors corresponding to Sawaya functional grade III (i.e., with an eloquent location within the motor or sensory cortex, or within the visual or speech centers [8]) than in cases of neoplasms of Sawaya functional grade I (i.e., with a noneloquent location in the frontal or temporal pole or the right parieto-occipital lobe) [15].

Minniti et al. [14] prospectively followed up 206 adult patients (median age 62 years, range 26–81 years) with 1–3 BM who underwent SRS for a total of 310 tumors. Marginal radiation doses (median 18 Gy) were delivered at the 80–90% isodose line and depended on the volume of the neoplasm, being 20, 18, and 15–16 Gy for lesions of <4.3 cc, 4.3–14.1 cc, and >14.1 cc, respectively. The exclusion criteria included a maximum tumor diameter >3.5 cm and prior radiation treatment. In 54% of patients, the KPS score before SRS was ≥70, and the majority of patients (61%)

Table 1 Summary of prospective studies on the risk of seizures in patients with brain metastases (BM) after stereotactic radiosurgery (SRS)

	Studies			
Study parameters	Chitapanarux et al. [12]	Lutterbach et al. [13]	Williams et al. [15]	Minniti et al. [14]
Inclusion criteria	1–4 BM; KPS score ≥60	1–3 BM, each with a maximum diameter ≤3 cm; KPS score ≥50	1–2 BM treated with SRS	1–3 BM treated with SRS
Exclusion criteria	Small cell lung cancer or lymphoma	Prior SRS/WBRT	Prior SRS/WBRT	Prior SRS/WBRT; BM with a maximum diameter >3.5 cm
Cohort size	41 patients	101 patients	273 patients	206 patients
Length of follow-up	Median 7 months (range 1.5–31)	Median 7.6 months	Median 19.9 months (range 1.0–90.8)	Median 9.4 months (range 2–42)
Age of patients	Median 55 years (range 30–75)	Mean 59 years (range 29–80)	Median 57 years (range 12–93)	Median 62 years (range 26–81)
KPS score	Median 90 (range 60–100)	≥70 in 81% of patients	Median 90 (range 40–100)	≥70 in 54% of patients
Primary site cancer control	In 51% of patients	In 67% of patients	ND	ND
Extracranial metastasis	Absent in 35% of patients	Absent in 39% of patients	ND	Stable extracranial disease in 44% of patients
Primary cancer histology	Lung cancer 37%, renal cancer 32%, melanoma 16%, breast cancer 10%, other cancer 5%	Lung cancer 27%, breast cancer 20%, renal cancer 15%, melanoma 12%, gastrointestinal cancer 12%, urogenital cancer 6%, other cancer or unknown origin 8%	Lung cancer 36%, melanoma 25%, renal cancer 17%, breast cancer 13%, sarcoma 2%, other cancer 7%	Lung cancer 51%, breast cancer 18%, melanoma 17%, other cancer 14%
Median marginal dose	18 Gy	18 Gy	18 Gy	18 Gy
Seizure occurrence	In 9 patients (22%)	In 9 patients (9%)	In 41 patients (15%)	In 16 patients (8%)

KPS Karnofsky Performance Scale, *ND* no data, *WBRT* whole-brain radiation therapy

presented with one BM. The median volume of the intracranial tumors was 2.81 cc (range 0.2–23.7 cc). No information was provided with regard to primary site cancer control, whereas stable extracranial disease by the time of SRS was noted in 44% of patients. Lung cancer was the most common source of BM (in 51% of cases), followed by breast carcinoma (in 18% of cases) and melanoma (in 17% of cases). Within a median follow-up period of 9.4 months (range 2–42 months) after SRS, a total of 16 patients (8%) had seizures [14].

Efficacy of Prophylactic Antiepileptic Therapy in Patients with Brain Metastases After Radiosurgery

Petrovich et al. [16] conducted a retrospective analysis of 458 patients (median age 57 years, range 21–90 years) with BM who underwent Gamma Knife radiosurgery (with a median marginal dose of 18 Gy) for a total of 1305 tumors. The selection criteria for SRS included 1–3 or 1–5 intracranial tumors in cases without and with prior whole-brain radiation therapy (WBRT), respectively; a histological confirmation of a cancer diagnosis; a lesion diameter ≤3.5 cm; and a KPS score ≥70. No information was provided with regard to the median KPS score of the cohort, primary site cancer control, and the presence of extracranial metastases. The majority of patients (58%) presented with one BM. The median volume of the intracranial tumors was 0.9 cc (range 0.1–40.3 cc). Melanoma was the most common source of BM (in 50.4% of cases) followed by lung cancer (in 20.5% of cases), breast cancer (in 8.3% of cases), renal cancer (in 6.3% of cases), colon cancer (in 2.8% of cases), and other cancers (in 11.7% of cases). During a median follow-up period after SRS of 9 months (range 3–84 months), a total of 13 patients (2.8%) had symptomatic epilepsy. Importantly, in nearly all of these cases, seizures occurred during the early phase of the study, prior to adaptation of routine short-course (<2 week) prophylactic antiepileptic therapy after SRS [16].

Patterns of Clinical Practice for Prophylactic Antiepileptic Therapy in Patients with Brain Metastases After Radiosurgery

Arvold et al. [17] conducted an internet-based survey of 500 randomly selected members of the American Society for Radiation Oncology (ASTRO) and received responses from 161 of them (32%). Overall, 79% of the respondents reported that they "never" or "rarely" gave AED to patients treated with SRS, 11% did so "sometimes," and 10% "usually" or "always" administered AED in such cases. The most common medication used was levetiracetam (64.6%), followed by phenytoin (29.2%), phenobarbital (4.2%), and lorazepam (2.1%). Of the respondents who used AED, 22.4% prescribed them for 1–3 days, 12.2% did so for 4–6 days, 24.5% for 7–14 days, 26.5% for 15–21 days, and 14.3% for >21 days. The major reason for prophylactic AED use after SRS was the provider's perception of a high risk of seizures [17].

Discussion

On the basis of the evaluated reports on prospective studies presented herein, the estimated risk of epilepsy in patients with BM treated with SRS ranges from 8% to 22% [12–15]. This seizuer risk is remarkably similar to those reported for patients with BM in the pre- [5, 18] and post-surgical setting [19–21]. This observation suggests that SRS unlikely increase seizure risk. However, several caveats about this interpretation should be noted. First, in most cases, surgery for BM is followed by adjuvant radiation treatment (either WBRT or SRS to the resection cavity); thus, the true rates of epilepsy in nonirradiated patients with BM remain poorly characterized. Second, the seizure risk may depend on the tumor location [15], and it is conceivable that it may be elevated if SRS is performed for select tumors (e.g., within the motor cortex). Finally, predisposition to seizures after therapeutic irradiation of intracranial neoplasms may be modified by the specific clinical context [22]. Nevertheless, the available data indicate that such clinical scenarios are relatively unusual. Our analysis suggests that prolonged prophylactic use of AED after SRS for BM in patients without a history of epilepsy is not generally justified—especially after considering the possible side effects of such treatment [4]. The available literature shows that most clinicians do not prescribe AED for prophylactic use after SRS [17].

Another important finding of the present analysis is that the incidence of epilepsy after SRS for BM did not depend on the overall length of follow-up. This finding suggests that seizures usually occur early after radiation treatment; presumably, therefore, a short course of prophylactic antiepileptic therapy after brain irradiation may sometimes be reasonable. The retrospective study by Petrovich et al. [16] supports such treatment, at least for selected patients deemed at high risk of seizures during or after SRS (e.g., after irradiation of a tumor within the motor cortex), as it may reduce the incidence of this adverse effect (according to class III evidence). Use of newer-generation AED for this purpose (e.g., levetiracetam) should be considered, given their minimal side effects during short-term administration [23]. In their series, Gokhale et al. [24] evaluated a 7-day course of levetiracetam prescribed after craniotomy for brain tumor resection, and noted only a mild adverse effect (somnolence) in approximately 4% of the treated patients, which resolved fully after discontinuation of the drug. As such, judicious consideration of AED in a subset of SRS-treated patients with BM may be warranted.

Conclusion

The incidence of seizures after SRS for BM varies from 8% to 22%, and there is no evidence that this treatment increases the incidence of symptomatic epilepsy in the general population of these patients. Therefore, routine administration and prolonged prophylactic use of AED in such cases in the absence of a seizure history is not recommended. Nevertheless, short-course prophylactic antiepileptic therapy may be considered in selected high-risk individuals.

Acknowledgements Dr. Wali was funded through a National Institutes of Health (NIH) TL1 predoctoral grant (#1TL1TR001443).

Conflict of Interest The authors have no conflict of interest concerning the reported materials or methods.

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Cumulative Intracranial Tumor Volume as a Prognostic Factor in Patients with Brain Metastases Undergoing Stereotactic Radiosurgery

Brian R. Hirshman, Jason Compton, Kate T. Carroll, Mir Amaan Ali, Sonya G. Wang, and Clark C. Chen

Abstract Approximately 25–35% of all cancer patients suffer from brain metastases (BM), and many of them—in particular, those with a limited number of intracranial tumors—are treated with stereotactic radiosurgery (SRS). Accurate prediction of survival remains a key clinical challenge in this population. Several prognostic scales have been developed to facilitate this prognostication, including the Recursive Partitioning Analysis (RPA) classification, the modified Recursive Partitioning Analysis (mRPA) subclassifications, the Basic Score for Brain Metastases (BS-BM), the Score Index for Radiosurgery (SIR), the Graded Prognostic Assessment (GPA), and the diagnosis-specific Graded Prognostic Assessment (dsGPA). However, none of these scales include consideration of the cumulative intracranial tumor volume (CITV), which is defined as the sum of all intracranial tumor volumes. Since there is mounting evidence that the CITV carries significant prognostic value in SRS-treated patients with BM, this variable should be considered during survival prognostication, along with other pertinent clinical, pathological, and molecular characteristics.

Keywords Basic Score for Brain Metastases · Cumulative intracranial tumor volume · Graded Prognostic Assessment · Intracranial metastases · Prognosis · Prognostic scales · Recursive Partitioning Analysis · Score Index for Radiosurgery · Stereotactic radiosurgery · Survival

B. R. Hirshman
Department of Neurosurgery, University of California San Diego (UCSD), La Jolla, CA, USA

J. Compton · K. T. Carroll · M. A. Ali
School of Medicine, University of California San Diego (UCSD), La Jolla, CA, USA

S. G. Wang
Department of Neurology, University of Minnesota Medical School, Minneapolis, MN, USA

C. C. Chen (✉)
Department of Neurosurgery, University of Minnesota Medical School, Minneapolis, MN, USA
e-mail: ccchen@umn.edu

Introduction

Approximately 25–35% of all cancer patients suffer from brain metastases (BM), but the true incidence of these neoplasms is likely underestimated. The incidence of BM exceeds that of the primary brain tumors [1–4]. As such, BM are the most common form of central nervous system (CNS) tumors in adults [1]. Since the population in developed countries is aging, and most solid organ cancers are diseases of the elderly, the total number of cancer cases is expected to increase in the coming years [5]. Paralleling the general incidence of cancer, the incidence of BM is also expected to rise. Moreover, many effective anticancer drugs (e.g., trastuzumab for breast cancer) do not cross the blood–brain barrier (BBB); as patients live longer with use of these agents, they are simultaneously at increased risk of developing BM. In this context, BM are expected to continue to be a growing public health concern.

Since most chemotherapeutic agents do not cross the BBB, treatment of BM has mainly relied upon surgical resection and/or irradiation. The latter, in particular, is a mainstay option for patients who are not candidates for surgery. Radiation treatment for patients with BM is typically given either as whole-brain radiation therapy (WBRT), where the cumulative dose is fractioned over an extended time period, or as stereotactic radiosurgery (SRS), which is delivered in one to five treatment sessions. Because WBRT is associated with an increased risk of neurocognitive deficits, the general practice pattern is to use SRS to treat patients afflicted with a limited number of BM [6–9]. SRS is usually delivered

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*,
Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_7,

either by the Gamma Knife, allowing for multiple radiation beams from stable cobalt 60 (^{60}Co) sources to converge on the target, or by a linear accelerator (LINAC), typically using volumetric modulated arc therapy (VMAT).

Although the overall survival (OS) of patients with BM remains poor, the proportion of those who survive for 1 year or longer is steadily increasing. Treatment options, including surgical intervention and SRS, should be considered on the basis of survival expectation. To facilitate clinical decision-making, multiple prognostic scales have been developed [10–17]. However, most of these models do not include consideration of the tumor volume. Here, we describe and compare various prognostic scales for SRS-treated patients with BM, review the emerging literature on the prognostic importance of the cumulative intracranial tumor volume (CITV)—defined as the sum of all BM volumes measured on postcontrast T1-weighted magnetic resonance imaging (MRI)—and discuss opportunities for future research.

Prognostic Scales for Radiosurgery-Treated Patients with Brain Metastases

The main prognostic scales for SRS-treated patients with BM include the Recursive Partitioning Analysis (RPA) classification [10], the modified Recursive Partitioning Analysis (mRPA) subclassifications [12, 17], the Basic Score for Brain Metastases (BS-BM) [11], the Score Index for Radiosurgery (SIR) [15, 16], the Graded Prognostic Assessment (GPA) [13], and the diagnosis-specific Graded Prognostic Assessment (dsGPA) [14, 18]. A summary of them is presented in Table 1. All of these schemes have been developed by means of retrospective statistical analysis. While the specifics of the scales differ, they generally use the same prognostic variables—namely, the patient's age, the Karnofsky Performance Scale (KPS) score, the systemic disease status (primary cancer control and/or the presence of extracranial metastases), the number of BM, and, in the case of the SIR, the largest intracranial tumor volume (LITV) [8].

Caveats About Terminology

It should be noted that the term "prognosis" for prediction of OS in SRS-treated patients with BM is defined loosely. "Prognosis" in modern medicine implies knowledge of the natural history of the disease in the absence of treatment. In contrast, "prediction" means knowledge of the likelihood of a response to therapeutic interventions. However, in cases of BM, it has often remained unclear whether survival patterns are secondary to the natural history of the disease or determined by the therapeutic response, which is variable. In particular, for patients who die within 6 months after SRS, it is difficult to determine whether death resulted from systemic cancer progression or was caused by progression of BM [19]. On the other hand, since OS >6 months without radiation treatment is uncommon in patients with BM, studies with 1-year OS as an endpoint are more likely to capture the likelihood of a therapeutic response. Technically, scales developed in this context should not be defined as "prognostic" but instead considered "predictive." Despite these caveats, the term "prognosis" has persisted in the SRS literature on studies that aim to characterize survival expectations. This broad definition has been adopted herein as well.

The Recursive Partitioning Analysis Classification

The RPA is a statistical method based on step-by-step classification of data using predictive variables with creation of a hierarchy or a regression tree [20, 21]. Gaspar et al. [10] applied this technique for combined evaluation of 15 prognostic factors, demonstrating significant associations with OS in 1200 patients with BM who underwent various WBRT regimens while enrolled in three consecutive Radiation Therapy Oncology Group (RTOG) trials (RTOG 7916, 8528, and 8905). The resultant classification is dependent on four parameters: at the apex of the recursive tree is the KPS score, followed by primary cancer control, the patient's age, and the presence of extracranial metastasis. These factors define three RPA classes. Patients with a KPS score ≥70, with controlled primary cancer, aged <65 years, and without extracranial metastases constitute the most favorable RPA class I group (with a median OS of 7.1 months). Those with a KPS score <70 comprise the most unfavorable RPA class III group (with a median OS of 2.3 months). All other individuals are combined within the intermediate RPA class II group (with a median OS of 4.2 months) [10].

Despite its simplicity, the RPA classification has been validated by multiple independent studies published over two decades [6, 9, 11–13, 16, 17, 22–24]. A weakness of this scale involves its lack of a rigorous definition for primary cancer control, which was historically defined by the RTOG as an absence of local–regional tumor progression (without consideration of at least a partial response to treatment [25]) at the time of clinical evaluation immediately prior to SRS. However, an absence of macroscopic growth does not necessarily imply tumor control. In addition, the interval between the last clinical evaluation before SRS and the actual treatment date requires specification, since progression of the primary neoplasm can occur during this time period [26].

Table 1 Summary of the main prognostic scales used in radiosurgery-treated patients with brain metastases (BM)

	Prognostic scales						
		mRPA subclassifications					
Characteristics	RPA classification [10]	For RPA class II [17]	For RPA class III [12]	BS-BM [11]	SIR [15, 16]	GPA [13]	dsGPA [14][g]
Year of publication	1997	2012	2002	2004	1998, 2000	2008	2010
Cohort size	1200 patients	2000 patients	408 patients	110 patients	65 patients	1960 patients	4259 patients
Treatment of BM within the evaluated cohort	Various WBRT regimens with or without a local FRT boost or concurrent BUdR	GKS either as a primary treatment or after previous tumor resection, WBRT, local FRT, SRS, or their combinations	WBRT with or without previous tumor resection	GKS either as a primary treatment or after previous tumor resection or WBRT	LINAC-based SRS	Various WBRT regimens with or without a local FRT or SRS boost, or concurrent BUdR	WBRT, SRS, or their combination with or without previous tumor resection
Number of assessed prognostic variables	4	4	3	3	5	4	From 1 to 4 (depending on the specific diagnosis)
Age groups	<65 years (class I), ≥65 years (class II), any age (class III)[d]	≥65 years[e]	<65 versus ≥65 years	NA	≤50 years (2 points), 51–59 years (1 point), ≥60 years (0 points)	<50 years (1 point), 50–59 years (0.5 points), >60 years (0 points)	<50 years (1 point)[a], 50–60 years (0.5 points)[a], >60 years (0 points)[a]
KPS score groups	≥70 (classes I or II), <70 (class III)	90–100 (0 points), 70–80 (1 point)	<70[f]	80–100 (1 point), 50–70 (0 points)	>70 (2 points), 60–70 (1 point), ≤50 (0 points)	90–100 (1 point), 70–80 (0.5 points), <70 (0 points)	90–100 (1 point)[b], 70–80 (0.5 points)[b], <70 (0 points)[b]; 100 (4 points)[c], 90 (3 points)[c], 80 (2 points)[c], 70 (1 point)[c], <70 (0 points)[c]
Primary cancer control	Yes (class I), no (class II), any (class III)[d]	Yes (0 points), no (1 point)	Yes versus no	Yes (1 point), no (0 points)	NA (as a separate variable)	NA	NA
Systemic disease status	NA (as a separate variable)	NA (as a separate variable)	NA (as a separate variable)	NA (as a separate variable)	CR-NED (2 points), PR-SD (1 point), PD (0 points)	NA (as a separate variable)	NA (as a separate variable)

(continued)

Table 1 (continued)

Characteristics	Prognostic scales						
		mRPA subclassifications					
	RPA classification [10]	For RPA class II [17]	For RPA class III [12]	BS-BM [11]	SIR [15, 16]	GPA [13]	dsGPA [14][g]
Presence of extracranial metastases	No (class I), yes (class II), any (class III)[d]	No (0 points), yes (1 point)	NA	No (1 point), yes (0 points)	NA (as a separate variable)	No (1 point), yes (0 points)	No (1 point)[a], yes (0 points)[a]
Number of BM	NA	1 (0 points), >1 (1 point)	1 versus >1	NA	1 (2 points), 2 (1 point), ≥3 (0 points)	1 (1 point), 2–3 (0.5 points), >3 (0 points)	1 (1 point)[b], 2–3 (0.5 points)[b], >3 (0 points)[b]
Largest brain tumor volume	NA	NA	NA	NA	<5 cc (2 points), 5–13 cc (1 point), >13 cc (0 points)	NA	NA
Resulting parameter	Discrete (3 classes)	Continuous (from 0 to 4 points) with further grouping (3 classes)	Discrete (3 classes)	Continuous (from 0 to 3 points)	Continuous (from 0 to 10 points) with further grouping	Continuous (from 0 to 4 points) with further grouping	Continuous (from 0 to 4 points) with further grouping
Median OS	Class I: 7.1 months, class II: 4.2 months, class III: 2.3 months	0 points: 19.7 months, 1 point: 15.6 months, 2 points: 8.4 months, 3 points: 5.2 months, 4 points: 3.5 months; class II-a (0–1 points): 15.4 months, class II-b (2 points): 8.4 months, class II-c (3–4 points): 4.7 months	Class III-a (age <65 years, primary cancer controlled, single brain metastasis): 3.2 months, class III-b (patients not included in classes III-a and III-c): 1.9 months, class III-c (age ≥65 years, primary cancer uncontrolled, multiple BM): 1.2 months	3 points: OS rate 55% at 32 months of follow-up, 2 points: 13.1 months, 1 point: 3.3 months, 0 points: 1.9 months	8–10 points: 31.4 months, 4–7 points: 7.0 months, 1–3 points: 2.9 months	3.5–4 points: 11.0 months, 3 points: 6.9 months, 1.5–2.5 points: 3.8 months, 0–1 points: 2.6 months	3.5–4 points: 13.2–18.7 months[h], 3 points: 6.9–16.9 months[h], 1.5–2.5 points: 4.4–9.4 months[h], 0–1 points: 2.8–6.1 months[h]

BS-BM Basic Score for Brain Metastases, *BUdR* bromodeoxyuridine, *CR* complete clinical remission, *dsGPA* diagnosis-specific Graded Prognostic Assessment, *FRT* fractionated radiotherapy, *GKS* Gamma Knife surgery, *GPA* Graded Prognostic Assessment, *KPS* Karnofsky Performance Scale, *LINAC* linear accelerator, *mRPA* modified Recursive Partitioning Analysis, *NA* not assessed, *NED* no evidence of disease, *OS* overall survival, *PD* progressive disease, *PR* partial remission, *RPA* Recursive Partitioning Analysis, *SD* stable disease, *SIR* Score Index for Radiosurgery, *SRS* stereotactic radiosurgery, *WBRT* whole-brain radiation therapy

[a]As assessed in patients with non–small cell lung cancer and small cell lung cancer

[b]As assessed in patients with non–small cell lung cancer, small cell lung cancer, renal cell carcinoma, and melanoma

[c]As assessed in patients with breast cancer and gastrointestinal cancer

[d]RPA class III includes any patient with a KPS score <70

[e]This subclassification has been developed for the RPA class II cohort, which presumes the patient's age is ≥65 years

[f]This subclassification has been developed for the RPA class III cohort, which presumes the KPS score is <70

[g]The presented data correspond to those in the original publication [14] but do not consider subsequent updates

[h]The median survival depends on the specific diagnosis

Modified Recursive Partitioning Analysis Subclassifications

Several modified RPA subclassifications have been developed with the goal of improving survival prognostication.

Yamamoto et al. [17] aimed to better define the heterogeneous RPA class II cohort by applying a Cox proportional hazards model for stepwise analysis of nine clinical parameters (including the CITV) in 2000 patients with BM who underwent Gamma Knife surgery (GKS) at a single institution. The authors reported that OS in RPA class II patients could be stratified further by the KPS score (90–100 versus 70–80), the number of BM (single versus multiple), primary cancer control (yes versus no), and the presence of extracranial metastases (no versus yes). Each variable is assigned 0 points or 1 point (for favorable and unfavorable survival associations, respectively), and the resulting score reflects the sum of the points (from 4 to 0). Of note, in contrast to the other main prognostic scales, a higher score in this mRPA subclassification indicates a worse prognosis. On the basis of this system, patients were grouped as RPA classes II-a (0–1 points), II-b (2 points), and II-c (3–4 points), and their median OS durations were 15.4, 8.4, and 4.7 months, respectively [17]. The validity of this scale for survival prognostication was confirmed in an independent cohort of 1753 patients treated at another institution [17], as well as in a subsequent study [24]. The major criticism was that the OS of patients within the RPA class I and II-a groups appeared comparable [24].

Using multivariate Cox proportional hazards analysis, Lutterbach et al. [12] stratified RPA class III patients into three subgroups. The most favorable prognosis (median OS 3.2 months) was noted in the RPA class III-a group (age <65 years, controlled primary tumor, single BM), and the most unfavorable prognosis (median survival 1.2 months) was observed in the RPA class III-c group (age ≥65 years, uncontrolled primary tumor, multiple BM). All RPA class III patients not classified as RPA class III-a or class III-c were lumped into the category of RPA class III-b (median OS 1.9 months) [12].

The Basic Score for Brain Metastases

Lorenzoni et al. [11] described the BS-BM scale, which was derived from a multivariate Cox proportional hazards model of ten clinical variables from 110 GKS-treated patients. The prognostic factors identified in this analysis (the KPS score, primary cancer control, and the presence of extracranial metastases) were given equal weight and assigned either 0 points or 1 point for unfavorable and favorable survival associations, respectively. The sum of the points (from 0 to 3) forms the BS-BM, in which higher values indicate a better prognosis; the median OS durations were 1.9, 3.3, and 13.1 months in cases with BS-BM of 0, 1, and 2 points, respectively. The observation that age was not a prognostic factor in this analysis is notable, since nearly all other studies have consistently demonstrated otherwise [23]. The authors also compared the accuracy of survival prognostication by the BS-BM, RPA classification, and SIR, and they found that the BS-BM was particularly effective for identifying patients with short OS after SRS. In addition, this analysis demonstrated a statistically significant association between a greater number of BM and the presence of extracranial metastases, and an inverse association between the LITV and the KPS score of the patient [11]. The limited size of the study cohort likely accounted for the failure to identify age, the LITV, and the number of BM as prognostic factors associated with survival.

The efficacy of the BS-BM for OS and systemic disease-free survival prognostication was verified subsequently by other investigators [13, 17, 24, 27].

The Score Index for Radiosurgery

The SIR was developed by Weltman et al. [15, 16] on the basis of Cox proportional hazards analysis of five clinical factors (the patient's age, KPS score, systemic disease status, number of intracranial tumors, and LITV) derived from SRS-treated patients with BM. Each variable was given equal weight and assigned 0, 1, or 2 points for unfavorable, intermediate, and favorable survival associations, respectively. The sum of the points (from 0 to 10) forms the SIR, in which higher values indicate a better prognosis; in cases with overall scores of 1–3, 4–7, and 8–10 points, the median OS durations were 2.9, 7.0, and 31.4 months, respectively [16]. Of note, for the first time, this model introduced the concept that the tumor volume is an important prognostic factor in SRS-treated patients with BM; however it used the LITV instead of the CITV.

The prognostic value of the SIR was validated by subsequent independent studies [8, 11, 13, 17, 24]. In contrast to other prognostic scales, it is predictive not only for OS but also for "qualitative survival" (defined as preservation of neurological function, providing a KPS score ≥70) [24]. Nevertheless, the SIR has been criticized for its complexity, which limits routine clinical use of this scale, and for omission of rigorously defined criteria for assessing the systemic disease status.

The Graded Prognostic Assessment

The GPA was designed by Sperduto et al. [13] specifically to exclude clinical variables that are difficult to quantify, such as systemic disease control. The scale was developed using

multivariate Cox proportional hazards analysis of 1-year survival data from five RTOG studies (RTOG 7916, 8528, 8905, 9104, and 9508). Instead of equal weighting of all prognostic factors, the relative magnitude of the hazard ratio (HR) was used to weight the GPA parameters. Each variable was assigned 0 points, 0.5 points, or 1 point for unfavorable, intermediate, and favorable survival associations, respectively. The sum of the points (from 0 to 4), in which higher values indicate a better prognosis, showed a significant association with the survival of patients; the median OS durations were 2.6, 3.8, 6.9, and 11.0 months in cases with GPA scores of 0–1, 1.5–2.5, 3, and 3.5–4 points, respectively. In addition, the authors reported that the prognostic accuracy of the GPA was comparable to that of the RPA classification and superior to those of the SIR and BS-BM [13].

The utility of the GPA in survival prognostication was validated in several subsequent studies [17, 23, 24]. Its relative limitations include omission of consideration of the intracranial tumor volume and the histology of the primary cancer.

The Diagnosis-Specific Graded Prognostic Assessment

In subsequent work, Sperduto et al. [14] developed the dsGPA to account for variability in survival patterns among patients with BM originating from different cancers. The fundamental concept underlying this system is that prognostic variables applicable to one tumor type (e.g., breast cancer) may not necessarily apply to another (e.g., melanoma). The methodology used to create the dsGPA was essentially the same as that used for the GPA, except that the analysis was histology specific. Six different groups of BM—originating from non–small cell lung cancer (NSCLC), small cell lung cancer (SCLC), melanoma, renal cell carcinoma (RCC), breast cancer, and gastrointestinal (GI) cancer—were assessed, and for each type of neoplasm, a distinct dsGPA was designed. For example, the scale for NSCLC and SCLC included four factors: the patient's age, the KPS score, the number of BM, and the presence of extracranial metastases. In contrast, the dsGPA for melanoma and RCC comprised only two parameters (the KPS score and the number of BM), whereas the dsGPA for breast and GI cancers considered only the KPS score. As with the original dsGPA, the prognostic variables were assigned weighted points, whose sum (from 0 to 4) forms the basis for prognostication, with higher values indicating better survival [14].

The dsGPA should be recognized as the first scale to define distinct prognostic factors in patients with BM of different cancers. Its utility in survival prognostication was validated in subsequent independent studies [6, 9, 18, 23, 28–31]. Moreover, several updates and modifications have been suggested for the originally developed prognostic schemes. For example, the current dsGPA for breast cancer includes molecular information (e.g., the estrogen receptor (ER) status, progesterone receptor (PR) status, and human epidermal growth factor receptor type 2 (HER2) status), allowing evidence-based choice of the optimal treatment strategy in each individual patient.

Prognostic Value of the Cumulative Intracranial Tumor Volume

An increased tumor burden, as reflected by a larger neoplasm volume, is associated with worse survival of patients with most solid cancers and is considered one of the main factors in staging [32, 33]. There is no reason to expect that these observations would not be applicable to intracranial tumors. Additionally, there are several other fundamental reasons why the CITV likely carries important prognostic information in patients with BM. First, the radiation dose during SRS generally represents an inverse function of the target volume; thus, dose de-escalation may be required in cases with a larger CITV to minimize the risk of neurotoxicity, especially if the neoplasms are critically located and affect highly eloquent brain structures [8, 23, 34–36]. Since the efficacy of SRS for BM is largely dependent on the radiation dose, one would expect that the CITV would also be associated with tumor control. Second, because the skull contains a rigidly fixed volume, a larger intracranial tumor burden results in displacement of the normal brain tissue. This phenomenon is known as the mass effect, and an increase in it is associated with a higher risk of a neurological deficit and poor survival [34]. In our series of patients with BM of RCC, melanoma, and GI cancer, the CITV inversely correlated with the KPS score [28–30]. Finally, a greater CITV may reflect more aggressive biology of the metastasizing cancer cells—in particular, their higher proliferative potential [8, 23], which also negatively impacts OS of patients.

The Cumulative Intracranial Tumor Volume Versus the Largest Intracranial Tumor Volume

There are strong theoretical arguments suggesting that the CITV may be superior to the LITV as a prognostic variable in patients with BM. In 50–70% of cases, multiple BM are observed at presentation; thus, the CITV may provide a better characterization of the disease process [8, 22, 23]. While in the case of a single BM, the CITV and LITV are equal, these parameters differ significantly in the majority of patients with

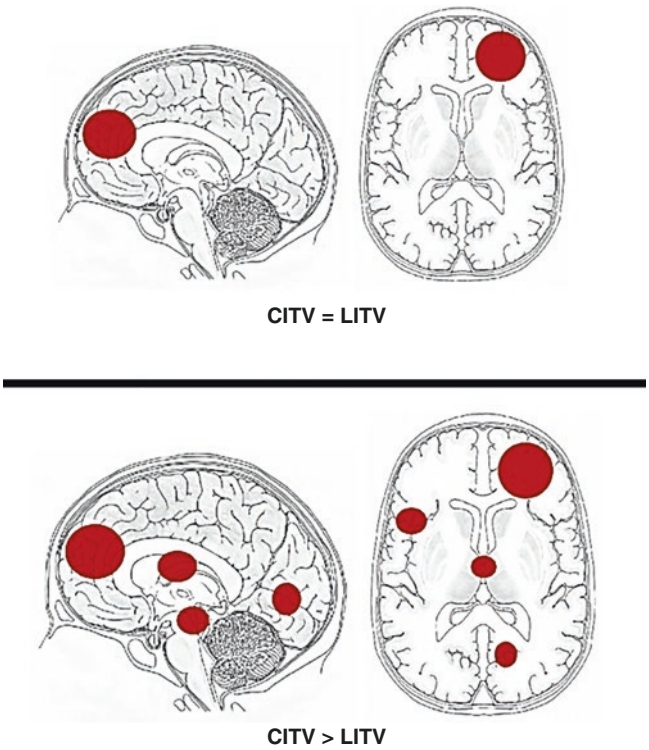

Fig. 1 Clinical examples with a cumulative intracranial tumor volume (CITV) equal to (*upper*) or larger than (*lower*) the largest intracranial tumor volume (LITV), as observed in cases of single and multiple intracranial neoplasms, respectively. The CITV is defined as the sum of the volumes of all brain metastases; thus, it includes the LITV

multiple BM (Fig. 1). In our series of >5500 patients, the CITV was at least 50% greater than the LITV in approximately 80% of cases [8]. Of note, the CITV may correlate with the number of BM (as in cases of RCC or melanoma), or it may not (as in cases of lung cancer), because of variability in the volumes of different intracranial tumors [28, 29, 31]. In addition, the CITV may characterize an underlying cancer biology not captured by the LITV; for instance, the molecular pathophysiology of neoplastic cells that give rise to one dominant and three smaller BM may differ from that in cases of four BM of similar sizes, and the responses to irradiation may differ accordingly. Our study indicated that the CITV may reflect the intracranial tumor burden better than the LITV and may be more efficient for survival prognostication [8].

Supportive Clinical Data

Several retrospective clinical studies have already shown the prognostic significance of the CITV in SRS-treated patients with BM, and it has been demonstrated that incorporation of this parameter into previously developed prognostic scales may increase their predictive efficacy (Table 2) [6, 8, 9, 22–24, 27, 34].

Bhatnagar et al. [22] reported the results of primary or salvage GKS with or without WBRT in 205 patients with ≥4 BM who underwent treatment at the University of Pittsburgh. The CITV (median 6.8 cc) was analyzed in a multivariate model along with other clinical and radiosurgical parameters, and it demonstrated the strongest association with OS, which was independent of the impact of the RPA class, the patient's age, and the marginal dose. This indicated that in cases of multiple BM, the prognostic values of the CITV and the RPA classification are complementary. In addition, in this study, the CITV was the only variable that showed a statistically significant association with local tumor control after irradiation [22].

Baschnagel et al. [6] evaluated 250 patients who underwent GKS at William Beaumont Hospital (Royal Oak, MI, USA). The CITV (either assessed as a continuous variable or dichotomized at several thresholds) demonstrated statistically significant associations with the OS of patients both in univariate analysis and in a multivariate model that included the patient's age, the KPS score, the presence of extracranial disease, and the number of BM. The optimal cutoff value of the CITV was identified as 2 cc (i.e., <2 versus ≥2 cc). The CITV was also significantly associated with OS when it was analyzed in a separate multivariate model along with the dsGPA score, which indicated the possible complementary roles of these parameters in survival prognostication. In this study, the number of BM was not predictive of OS if was assessed as a continuous variable, although it showed prognostic significance at some evaluated thresholds (generally at ≤2 versus ≥3) in univariate analysis. In addition, a CITV ≥2 cc and the presence of extracranial disease were predictive of distant brain failure [6].

Similar results were reported by Likhacheva et al. [9], who evaluated 251 patients treated with primary GKS or LINAC-based SRS alone at the MD Anderson Cancer Center. The CITV, assessed as either a continuous variable or a categorical variable, demonstrated a statistically significant association with the OS of patients in univariate analysis and preserved its prognostic value after inclusion as a categorical variable (≤2 versus >2 cc) in a multivariate model along with the patient's age, the dsGPA score, the number of BM, and the presence of extracranial disease. Thus, this study also demonstrated the possible complementary roles of the CITV and dsGPA score in survival prognostication. Once again, the number of BM was not predictive of OS if it was assessed as a continuous variable, although it showed prognostic significance at some evaluated cutoff values in univariate analysis. Also, a CITV of >2 cc was significantly associated with the likelihood of poor local tumor control after SRS [9].

Gonda et al. [23], from our group, conducted a two-phase investigation with initial evaluation of 1017 patients from the University of California San Diego (UCSD) and subsequent validation of the results using an independent cohort

Table 2 Summary of selected clinical series demonstrating the prognostic significance of the cumulative intracranial tumor volume (CITV) in radiosurgery-treated patients with brain metastases (BM)

Study characteristics and results	Studies								
				Gonda et al. [23]				Hirshman et al. [8]	
	Bhatnagar et al. [22]	Baschnagel et al. [6]	Likhacheva et al. [9]	Study cohort	Validation cohort	Serizawa et al. [27]	Emery et al. [34]	Study cohort	Validation cohort
Study type	Retrospective, single institution	Retrospective, single institution	Retrospective, single institution	Retrospective, single institution	Retrospective, single institution	Retrospective, multi-institution	Retrospective, single institution	Retrospective, multi-institution	Retrospective, multi-institution
Cohort size	205 patients	250 patients	251 patients	1017 patients	2519 patients	2838 patients	300 patients	3061 patients	2793 patients
Treatment of BM within the evaluated cohort	Primary or salvage GKS with or without upfront or subsequent WBRT	Primary GKS alone	Primary GKS or LINAC-based SRS alone	Primary GKS or GKS after previous treatment, including upfront WBRT	Primary GKS or GKS after previous treatment, including upfront WBRT	Primary GKS or GKS after previous treatment, including upfront WBRT	Primary GKS or GKS after previous treatment, including upfront WBRT	Primary or repeat GKS	Primary or repeat GKS
Primary cancer location									
Breast	23%	13%	16%	22%	11%	11%	13%	11%	12%
Gastrointestinal	–	7%	–	–	12%	13%	26%	13%	9%
Lung	44%	66%	34%	45%	65%	66%	31%	66%	62%
Melanoma	17%	5%	29%	22%	–	–	23%	–	–
Renal cell carcinoma	6%	4%	8%	7%	4%	–		–	–
Other/ unspecified	10%	5%	13%	4%	8%	11%	6%	11%	17%
Number of BM	Multiple (≥4)	Single (in 53% of patients) and multiple (in 47% of patients)	Single and multiple	Single (in 39% of patients) and multiple (in 61% of patients)	Single (in 29% of patients) and multiple (in 71% of patients)	Single (in 28% of patients) and multiple (in 72% of patients)	Single (in 39% of patients) and multiple (in 61% of patients)	Single and multiple	Single and multiple
Type of CITV evaluation	As a categorical variable dichotomized at a median value of 6.8 cc	As continuous and categorical variables (dichotomized at various thresholds)	As continuous and categorical variables (dichotomized at various thresholds)	As continuous and categorical variables (dichotomized at various thresholds)	As continuous and categorical variables (dichotomized at various thresholds)	As a categorical variable dichotomized at a cutoff value of 15 cc	As a continuous variable	As continuous and categorical variables (comprising 3 groups)	As continuous and categorical variables (comprising 3 groups)
CITV cutoff value used in the multivariate model	<6.8 versus >6.8 cc	<2 versus ≥2 cc	≤2 versus >2 cc	≤4 versus >4 cc	≤4 versus >4 cc	≤15 versus >15 cc	–	<3.5 versus 3.5–13 versus >13 cc	<3.5 versus 3.5–13 versus >13 cc
Covariates evaluated in the multivariate OS model									
CITV	$P = 0.002$	$P = 0.008$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.0001$[e]	$P = 0.004$[a]	$P < 0.001$[b]	$P < 0.001$[b]
LITV	–	–	–	–	–	ND[e]	–	$P =$ NS[b]	$P =$ NS[b]
Age	$P = 0.005$	$P = 0.011$	$P = 0.002$	$P < 0.001$	$P < 0.001$	ND[e]	$P = 0.004$	$P = 0.001$[b]	$P =$ NS[b]

Sex	P = NS	–	–	–	–	–	P = NS	–	–
KPS score	P = NS	$P < 0.001$	–	$P < 0.001$	$P < 0.001$	ND[e]	P = NS	$P < 0.001$[b]	$P < 0.001$[b]
Systemic disease status	P = NS	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	–	$P < 0.001$	$P < 0.001$[b]	$P < 0.001$[b]
Number of treated BM	P = NS	P = NS	P = NS	$P < 0.001$	$P < 0.001$	$P = 0.0118$[e]	P = NS	$P < 0.001$[b]	$P < 0.001$[b]
Location of BM	–	–	–	–	–	–	$P < 0.001$	–	–
RPA class	$P = 0.009$	–	–	–	–	–	–	–	–
dsGPA score	–	$P < 0.001$[d]	$P < 0.001$	–	–	–	–	–	–
Primary cancer location	P = NS	–	–	$P < 0.001$	$P = 0.028$	ND[e]	$P < 0.001$	–	–
Previous WBRT	–	–	–	P = NS	P = NS	ND[e]	P = NS	–	–
Previous craniotomy	–	–	–	–	–	ND[e]	–	–	–
Chemotherapy	–	–	–	–	–	ND[e]	–	–	–
Presence of leptomeningeal dissemination	–	–	–	–	–	$P < 0.0001$[e]	–	–	–
Neurological symptoms	–	–	–	–	–	$P < 0.0020$[e]	–	–	–
Treatment time period	–	–	–	P = NS	–	–	–	–	–
Marginal dose	$P = 0.019$	–	–	–	–	–	P = NS	–	–
Prescription isodose	–	–	–	–	–	–	P = NS	–	–
Impact of the CITV on OS after SRS	ND	HR for death 1.5 in cases with a CITV ≥2 cc[c]	HR for death 1.98 in cases with a CITV >2 cc[c]	HR for death 1.49 in cases with a CITV >4 cc[c]	HR for death 1.29 in cases with a CITV >4 cc[c]	HR for poor qualitative survival 1.94 and for neurological death 2.01 in cases with a CITV >15 cc[c]	HR for death 1.44 per 1-unit increase in the cube root of the cumulative volume of supratentorial tumors	HR for death 0.86 per CITV grouping increase[b]	HR for death 0.86 per CITV grouping increase[b]

dsGPA diagnosis-specific Graded Prognostic Assessment, *GKS* Gamma Knife surgery, *HR* hazard ratio, *KPS* Karnofsky Performance Scale, *LINAC* linear accelerator, *LITV* largest intracranial tumor volume, *ND* no data, *NS* not significant, *OS* overall survival, *RPA* Recursive Partitioning Analysis, *SIR* Score Index for Radiosurgery, *SRS* stereotactic radiosurgery, *WBRT* whole-brain radiation therapy

[a]Cumulative volume of supratentorial tumors

[b]According to Cox proportional hazards analysis with inclusion of the CITV in the SIR model

[c]According to multivariate analysis

[d]Analyzed in a separate multivariate model

[e]The multivariate model in this study was directed at assessment not of overall survival but of neurological survival

of 2519 patients from Katsuta Hospital (Hitachinaka, Japan). Multivariate analysis demonstrated nearly congruent results in both cohorts, with statistically significant associations between OS and the following variables: the patient's age, KPS score, systemic disease status, tumor histology, number of BM, and CITV. In this study, both the number of BM and the CITV were analyzed as continuous variables, dichotomized at various thresholds. A graded decrease in OS was observed to parallel increases in the number of BM or the CITV. There was no significant correlation between the number of BM and the CITV, and, as such, the authors suggested that these variables were independently associated with OS [1]. The optimal cutoff value of the CITV for survival prognostication was defined as 4 cc (i.e., ≤4 versus >4 cc), and this threshold was validated in several subsequent studies [28, 29, 31, 37].

Serizawa et al. [27] developed the Neurological Prognostic Score (NPS) for prediction of "qualitative survival" and a neurological cause of death (neurological survival). The authors analyzed 15 dichotomized prognostic variables in 2838 patients who underwent single-session, multisession, or staged GKS either as primary treatment or after previous treatment (including upfront WBRT) at the Chiba Cardiovascular Center (Ichihara, Japan) and the Tsukiji Neurological Clinic (Tokyo, Japan). The number of BM (>10 versus ≤10), the CITV (>15 versus ≤15 cc), MRI findings of leptomeningeal dissemination (yes versus no), and the presence of neurological symptoms (yes versus no) were verified in the multivariate model as the most significant combination of predictive factors. Each variable was assigned 0 points or 1 point for unfavorable and favorable survival associations, respectively. The resulting score, based on the sum of the points (from 0 to 4), was used for defining NPS subgroup A (3–4 points) and subgroup B (0–2 points), which were combined with both the standard BS-BM (termed the modified BS-BM) and the GPA to improve the prognostic accuracy of these scales [27]. It should be noted that this study used somewhat arbitrary cutoff values for dichotomizing the number of BM and the CITV.

Emery et al. [34] evaluated 300 patients who underwent GKS with or without previous treatment (including upfront WBRT) at the University of Virginia (Charlottesville, VA, USA). Multiple prognostic parameters were evaluated in the multivariate model, which revealed that the cumulative volume of supratentorial (but not infratentorial or brainstem) tumors was significantly and independently associated with the OS of patients. Other important prognostic factors were the patient's age, systemic disease status, tumor histology, and BM location [34].

To determine whether the prognostic value of the SIR may be improved by replacing the LITV with the CITV, our group performed a two-phase study with initial evaluation of 3061 patients and subsequent validation of the results using an independent cohort of 2793 patients treated with GKS at several institutions in the USA and Japan [8]. The CITV was separated into three groups (<3.5 versus 3.5–13 versus >13 cc) and compared with the LITV. A series of multivariate models demonstrated that the CITV was independently associated with OS in both investigated cohorts of patients and that inclusion of the CITV instead of the LITV in calculation of the SIR (termed the CITV-modified SIR) resulted in modest but statistically significant improvements in the sensitivity and specificity of this scale in predicting the 1-year survival of patients. Moreover, if the CITV and LITV were evaluated within the same model, only the former parameter preserved its statistically significant predictive power, reflecting its superiority as a prognostic indicator [8].

Incorporating the Cumulative Intracranial Tumor Volume into the Diagnosis-Specific Graded Prognostic Assessment

Several previous reports have highlighted the prognostic significance of the CITV in cases of specific cancers. For example, Bian et al. [7] retrospectively evaluated 401 patients with melanoma BM who underwent GKS at the University of Southern California (Los Angeles, CA, USA). CITV was assessed in a multivariate model as a categorical variable (<5 versus 5–10 versus >10 cc) and demonstrated a statistically significant independent association with OS, along with other factors such as the patient's age and sex, the number of BM, and the treatment time period. In this series, the strongest determinants of shortened OS were the presence of ≥5 BM (HR 2.2, $P < 0.001$) and a CITV >10 cc (HR 1.7, $P = 0.002$). The median OS durations of patients with CITV of <5, 5–10, and >10 cc were 8.2, 6.9, and 5.9 months, respectively. Moreover, a larger CITV and an absence of prior intracranial tumor resection were the only statistically significant factors associated with shortened OS in the subgroup of patients with multiple BM ($N = 213$) [7].

Subsequent work by our group showed that incorporation of the CITV into the dsGPA improved survival prognostication after SRS for BM of lung cancer [31], RCC [28], melanoma [29], and GI cancer [30] (Table 3). Importantly, in each of these studies, the validity of the CITV-modified prognostic scale was confirmed in independent cohorts of patients [28–31]. Notably, the optimal CITV threshold for prediction of OS may differ in specific cancers, which may in part be related to the intrinsic degree of radiosensitivity of the neoplasm [30]. Supporting this hypothesis, the CITV did not contribute to survival prognostication in patients with BM of breast cancer [38]—a tumor type that tends to be relatively radiosensitive.

Table 3 Summary of studies evaluating possible incorporation of the cumulative intracranial tumor volume (CITV) into the diagnosis-specific Graded Prognostic Assessment (dsGPA) scale for radiosurgery-treated patients with brain metastases (BM)

Study characteristics and results	Primary cancer (study)							
	Lung cancer (Marcus et al. [31])		Renal cell carcinoma (Ali et al. [28])		Melanoma (Hirshman et al. [29])		Gastrointestinal cancer (Joshi et al. [30])	
	Study cohort	Validation cohort	Study cohort	Validation cohort	Study cohort	Validation cohort	Study cohort	Validation cohort
Study type	Retrospective, single institution	Retrospective, single institution	Retrospective, multi-institution	Retrospective, single institution	Retrospective, multi-institution	Retrospective, multi-institution	Retrospective, multi-institution	Retrospective, single institution
Cohort size	365 patients	1638 patients	360 patients	107 patients	344 patients	201 patients	328 patients	390 patients
Treatment of BM within the evaluated cohort	GKS	GKS	Primary GKS	Primary GKS	GKS	GKS	Primary GKS	Primary GKS
Type of CITV evaluation	As a categorical variable	As a categorical variable	As a continuous and categorical variable	As a categorical variable	As a continuous and categorical variable	As a categorical variable	As a continuous and categorical variable	As a categorical variable
CITV cutoff value used in the multivariate model	>4 versus ≤4 cc	>4 versus ≤4 cc	≥4 versus <4 cc	≥4 versus <4 cc	≥4 versus <4 cc	≥4 versus <4 cc	≥12 versus <12 cc	≥12 versus <12 cc
Outcome measures	OS (median 7.0 months), 1-year OS rate	OS (median 7.5 months), 1-year OS rate	OS (median 6.0 months), 1-year OS rate (29.7%)	1-year OS rate	OS (median 4.0 months), 1-year OS rate (17.4%)	OS (mean 8 months), 1-year OS rate (33.0%)	OS (median 5.1 months), 1-year OS rate (19.2%)	OS (median 5.0 months), 1-year OS rate (18.0%)
HR for death according to univariate Cox proportional hazards analysis of the association between the CITV and OS	ND	ND	0.314 per CITV group point increase ($P = 0.007$)	ND	0.771 per CITV group point increase ($P < 0.001$)	0.750 per CITV group point increase ($P < 0.001$)	0.580 per CITV group point increase ($P < 0.001$)	0.661 per CITV group point increase ($P < 0.001$)
HR for death according to multivariate Cox proportional hazards analysis of the association between the CITV and OS	0.67 per CITV group point increase ($P = 0.001$)	0.68 per CITV group point increase ($P = 0.001$)	0.256 per CITV group point increase ($P = 0.042$)	ND	0.803 per CITV group point increase ($P = 0.008$)	0.799 per CITV group point increase ($P = 0.003$)	0.631 per CITV group point increase ($P < 0.001$)	0.713 per CITV group point increase ($P = 0.002$)
Covariates evaluated in multivariate Cox proportional hazards analysis along with the CITV (dsGPA parameters)	Age (>60 versus 50–60 versus <50 years), KPS score (<70 versus 70–80 versus 90–100), extracranial metastases (yes versus no), number of BM (>3 versus 2–3 versus 1)	Age (<50 versus 50–60 versus >60 years), KPS score (<70 versus 70–80 versus 90–100), extracranial metastases (yes versus no), number of BM (>3 versus 2–3 versus 1)	KPS score (<70 versus 70–80 versus 90–100), number of BM (>3 versus 2–3 versus 1)	KPS score (<70 versus 70–80 versus 90–100), number of BM (>3 versus 2–3 versus 1)	KPS score (<70 versus 70–80 versus 90–100), number of BM (>3 versus 2–3 versus 1)	KPS score (<70 versus 70–80 versus 90–100), number of BM (>3 versus 2–3 versus 1)	KPS score (<70 versus 70 versus 80 versus 90 versus 100)	KPS score (<70 versus 70 versus 80 versus 90 versus 100)
NRI value >0 with use of the dsGPA-CITV relative to the standard dsGPA	0.430 (95% CI 0.228–0.629, $P < 0.05$)	0.304 (95% CI 0.198–0.407, $P < 0.05$)	0.3156 (95% CI 0.0883–0.5428, $P = 0.0065$)	1.161 (95% CI 0.8412–1.4820, $P < 0.001$)	0.3662 (95% CI 0.1253–0.6072, $P = 0.0029$)	0.485 ($P = 0.002$)	0.397 (95% CI 0.165–0.630, $P < 0.001$)	0.478 (95% CI 0.257–0.699, $P < 0.001$)
IDI with use of the dsGPA-CITV relative to the standard dsGPA	0.029 (95% CI 0.004–0.073, $P < 0.05$)	0.007 (95% CI 0.001–0.018, $P < 0.05$)	0.0151 (95% CI 0.0036–0.0277, $P = 0.0183$)	0.1462 (95% CI 0.0710–0.2215, $P < 0.001$)	0.0238 (95% CI 0.0077–0.0398, $P = 0.0037$)	ND	0.019 (95% CI 0.004–0.033, $P = 0.013$)	0.028 (95% CI 0.014–0.043, $P < 0.001$)

CI confidence interval, *dsGPA-CITV* cumulative intracranial tumor volume–modified diagnosis-specific Graded Prognostic Assessment, *GKS* Gamma Knife surgery, *HR* hazard ratio, *IDI* integrated discrimination improvement, *KPS* Karnofsky Performance Scale, *ND* no data, *NRI* net reclassification improvement, *OS* overall survival

Future Directions

There are several key issues pertaining to the CITV that remain unclear. For instance, the available literature data on the prognostic value of this factor in SRS-treated patients with BM have been agnostic about variability in the intracranial tumor volume. It is evident, however, that two patients with four BM and similar CITV of 4 cc may show quite distinct profiles (e.g., four 1 cc tumors in patient 1 versus one 2.5 cc tumor plus three 0.5 cc tumors in patient 2). Whether such heterogeneity influences OS remains unknown. Another important variable that is likely associated with the prognosis after SRS for BM involve surgical resection of the intracranial neoplasm, which has demonstrated its positive effect on OS in selected series of patients (e.g., in cases of metastatic melanoma [7, 39]). Since surgery tends to be performed in cases of larger intracranial tumors, it may interact with the CITV in survival prognostication. These questions warrant further investigation.

With advances in genomics, cancers that were previously considered as a single histopathological entity have been increasingly stratified on the basis of their molecular pathophysiology (e.g., breast cancer has already been separated into distinct subgroups, which exhibit differential responses to selected medications). There is no doubt that molecular stratification of various tumors within the context of precision medicine, where therapeutic targets are tailored to the mutational and epigenetic landscape of the neoplasm, has transformed and will continue to transform the survival patterns of SRS-treated patients with BM. This process is magnified by the introduction of novel anticancer agents, including various immunotherapies and molecular targeted therapies, which are now increasingly being combined with radiation treatment. Therefore, future prognostic scales for BM will require integration of variables that account for the impact of such novel therapeutic trends.

Finally, from a methodological perspective, there have been significant advances in statistical science and informatics since the introductions of the RPA and the Cox proportional hazards model. Application of novel classification and regression tools (such as random forests analysis), coupled with machine-learning analytics (such as factorial analysis of mixed data), may facilitate development of more efficient prognostic scales. Of equal importance, clinicians should seek out opportunities for meaningful collaboration by integrating their data sets to maximize sample sizes and provide more effective opportunities for validation efforts. Until now, nearly all reports on verification of key prognostic scales have been based on retrospective analyses of previously collected data, while academic rigor definitely requires their prospective evaluation.

Conclusion

Compelling theoretical underpinnings and the available clinical data strongly support the prognostic significance of the CITV in SRS-treated patients with BM. Optimal clinical decisions require meaningful consideration of this factor in the context of other pertinent clinical, pathological, and molecular characteristics.

Conflict of Interest The authors have no conflict of interest concerning the reported materials or methods.

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Treatment Options for Leptomeningeal Metastases of Solid Cancers: Literature Review and Personal Experience

Takeshi Kondoh and Takashi Sonoda

Abstract Leptomeningeal metastases (LM) may complicate the clinical course of any solid cancer or hematological malignancy. Diagnosis of such cases requires a multifaceted approach, including careful evaluation of the clinical history, detailed neurological examination, advanced imaging studies, and related laboratory data analysis. Therapeutic options for management of LM have not been standardized yet. Conventional intrathecal chemotherapy with or without involved-field fractionated radiotherapy has only modest efficacy, and the prognosis of most patients remains grim. Therefore, development of new, more aggressive multimodal treatment strategies is definitely needed. Immune checkpoint inhibitors—in particular, molecular targeted therapy—have demonstrated promising results in selected groups of patients. There may be an important role for stereotactic radiosurgery as well. Because organization of prospective randomized multi-institutional trials on treatment of LM of solid cancers may be problematic, practical guidelines for optimal therapeutic strategies in such cases should be established on the basis of integrated results of small-scale prospective and retrospective studies.

Keywords Carcinomatous meningitis · Diagnosis · Fractionated radiotherapy · Immune checkpoint inhibitors · Intrathecal chemotherapy · Leptomeningeal carcinomatosis · Leptomeningeal metastases · Molecular targeted therapy · Outcome · Response assessment · Stereotactic radiosurgery · Treatment

T. Kondoh (✉)
Department of Neurosurgery, Shinsuma General Hospital, Kobe, Japan
e-mail: tkondo@med.kobe-u.ac.jp

T. Sonoda
Department of Oncology, Meiwa Hospital, Nishinomiya, Japan

Introduction

Leptomeningeal metastases (LM), which are also known as carcinomatous meningitis or meningeal carcinomatosis, refer to an extremely devastating form of central nervous system (CNS) involvement in oncological disease, characterized by neoplastic invasion of leptomeninges and dissemination of malignant cells throughout the cerebrospinal fluid (CSF). This may complicate the clinical course of any cancer or hematological malignancy, is encountered in 4–15% of patients with solid tumors (being most common in cases of breast and lung cancers, and melanoma), and may be identified in nearly 20% of autopsies if neurological manifestations have presented during the history of the oncological disease [1, 2]. Availability of advanced diagnostic modalities and increased patient survival due to better local and systemic control of cancer have resulted in greater awareness and increased recognition of LM [3]. Herein, we review the existing data on diagnosis, therapeutic options, and response assessment criteria in such cases, and present our personal experience with their management.

Diagnosis of Leptomeningeal Metastases

Diagnosis of LM requires careful evaluation of the clinical history, detailed neurological examination, advanced imaging studies, and related laboratory data analysis. Typical clinical signs include cauda equine syndrome, communicating hydrocephalus, and cranial neuropathies [4]. Analysis of a large cohort of patients ($N = 519$) revealed that diagnosis of LM was established by magnetic resonance imaging (MRI) alone in 35% of cases, by CSF cytology alone in 22%, and by their combination in 42% [5], emphasizing the importance of a multifaceted clinical approach. Of note, even in the absence of specific findings from MRI and CSF cytology,

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*,
Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_8,

the diagnosis of probable LM can be made in a patient with known cancer and typical neurological manifestations [4].

Magnetic Resonance Imaging

MRI may demonstrate focal or diffuse contrast enhancement of leptomeninges, nerve roots, and/or the ependymal surface, which are highly suggestive of LM and may eliminate the need for confirmatory cytological evaluation of CSF (Figs. 1 and 2). However, a normal radiological examination does not exclude the diagnosis, since negative neuroimaging findings may be encountered in 30–70% of patients with LM [4].

Cerebrospinal Fluid Examination

Evaluation of CSF—which typically demonstrates increased opening pressure, a high protein content, a decreased glucose level, and the presence of abnormal cells—may significantly facilitate detection of LM in clinical practice [4, 6–8]. Identification of neoplastic cells in CSF leads to a definitive diagnosis, but it is well recognized that the rate of false negative results from single cytological analysis is approximately 50% even when large-volume sampling is done and appropriate processing methods are utilized [7]. Repeated analysis increases the rate of malignant cell identification to ≥80% [4].

In addition to cytology, in an appropriate clinical context, assessment of specific tumor biomarkers in CSF may be helpful, especially if their serum-to-CSF ratios are significantly reduced [9]. For instance, carcinoembryonic antigen (CEA) may be present in CSF either because of direct accumulation resulting from production by metastatic cells within the CNS or because of diffusion from blood through an impaired blood–brain barrier (BBB) [10, 11]. Kang et al. [12] identified significantly higher levels of CEA in CSF from patients with LM (confirmed by the presence of neoplastic cells). It was suggested that a serum-to-CSF CEA ratio <60 has sufficiently high specificity for diagnosis of LM [9]. Recent studies have indicated that other tumor biomarkers (e.g., vascular endothelial growth factor (VEGF) and stromal cell derived factor 1 (SDF-1)) may also be helpful for detection of LM [13, 14], but their clinical utility still requires validation.

Diagnostic accuracy may be further increased by advanced methods of CSF analysis [14]. As has been reported, epithelial cell adhesion molecule (EpCAM)–based flow cytometry may be superior to CSF cytology for detection of LM in patients with known cancer, clinical indications of CNS involvement, and nonconclusive MRI examination results [15], while

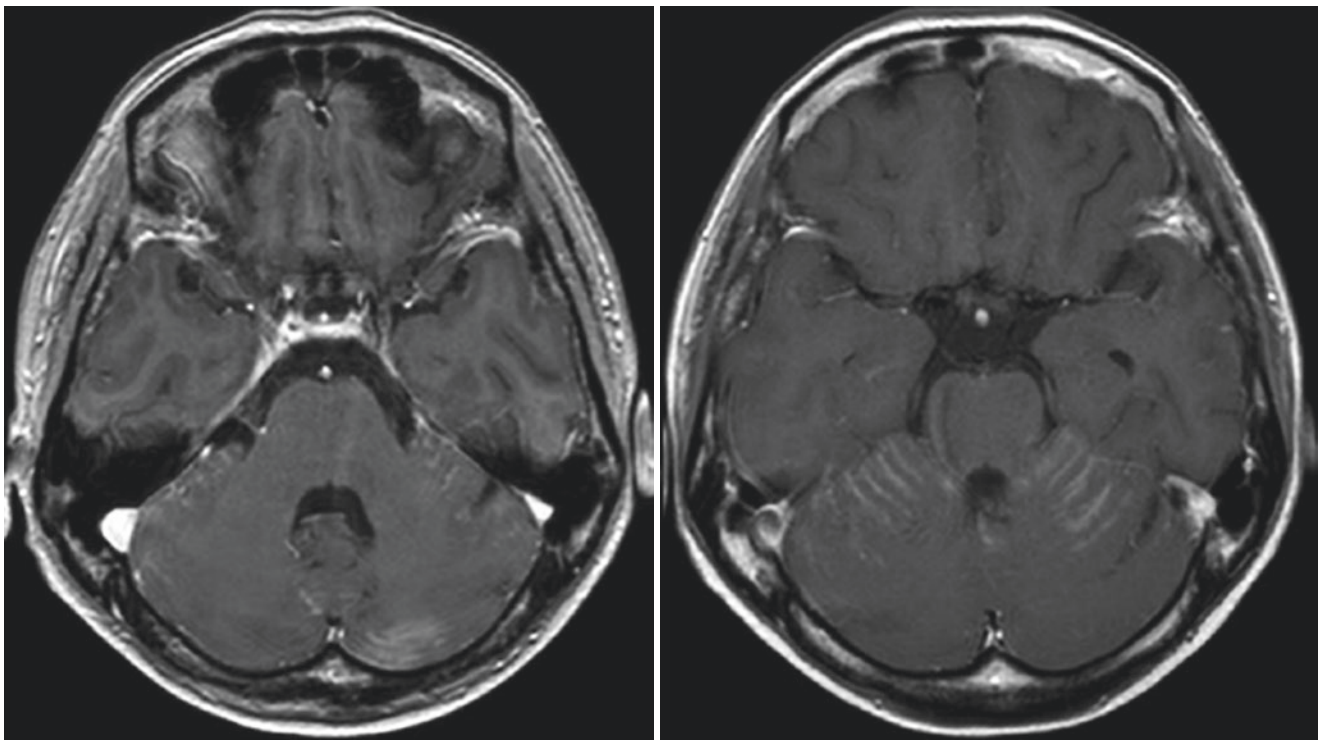

Fig. 1 Postcontrast T1-weighted magnetic resonance imaging in a 61-year-old woman with breast cancer, demonstrating diffuse bilateral enhancement of the cerebellar fissures. This strongly suggested leptomeningeal metastases and eliminated the need for confirmation of the diagnosis by cerebrospinal fluid cytology

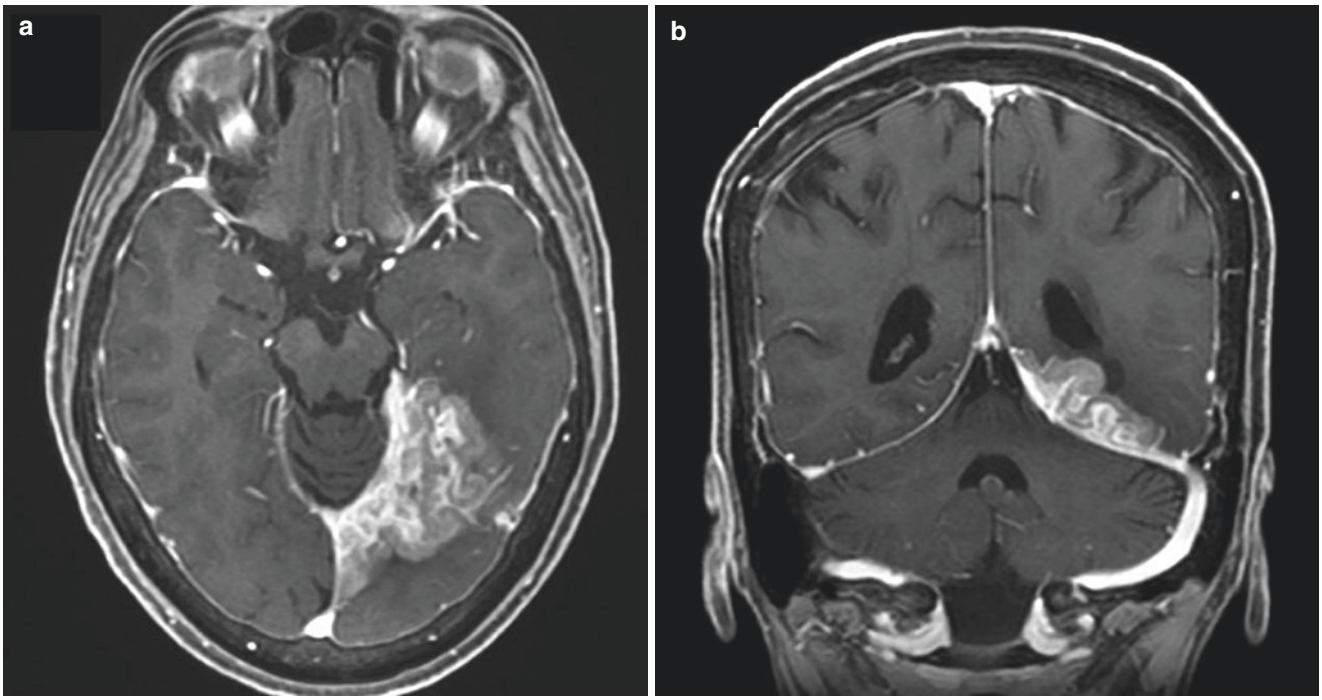

Fig. 2 Postcontrast T1-weighted axial (**a**) and coronal (**b**) magnetic resonance imaging in an 89-year-old woman with lung cancer who presented with a mild cognitive decline, demonstrating a heterogeneously enhanced irregular-shaped nodular mass on the left side of the tentorium with thickening of its adjacent part. This strongly suggested the presence of leptomeningeal metastases and eliminated the need for confirmation of the diagnosis by cerebrospinal fluid cytology

identification and counting of various neoplastic cells in CSF samples may be facilitated by fluorescence in situ hybridization (FISH) with immunostaining for tumor markers [16].

Therapeutic Options for Leptomeningeal Metastases

Therapeutic options for management of LM have not been standardized yet. For example, Chamberlain et al. [4] reviewed six randomized clinical trials on intrathecal chemotherapy published between 1987 and 2006. The methodology of these studies varied considerably with regard to pretreatment evaluations, types of therapy, and response assessments. The primary endpoints were highly heterogeneous and included overall survival (OS), the neurological response rate, the time to neurological progression, and progression-free survival (PFS). The secondary endpoints were even more variable and comprised OS, LM-specific survival, the neurological response rate, time to neurological progression, evolution of the Karnofsky Performance Scale (KPS) score over time, quality of life (QOL), safety and toxicity profiles, and the cause of death. The response criteria were based on combinations of clinical data, neuroimaging, and CSF cytology, and differed from one study to another. The authors concluded that there is a significant unmet need for guidelines for evaluation and treatment of patients with LM [4].

Systemic Chemotherapy

The effectiveness of systemic chemotherapy for LM remains unknown, and it is usually not considered a primary treatment option in such cases, although it is still frequently given to patients because they have active systemic cancer [4]. Of note, CSF exposure to most antitumor agents is <5% of their plasma concentration; thus, it is doubtful whether systemic treatment would actually provide benefits additional to those of a combination of intrathecal chemotherapy and fractionated radiotherapy (FRT) for LM [17]. Moreover, a combination of systemic and intrathecal chemotherapy may be associated with higher toxicity. However, administration of systemic chemotherapy after effective control of CNS disease may be reasonable, since it may potentially increase treatment efficacy and improve the prognosis [17].

Intrathecal Chemotherapy

Intrathecal chemotherapy plays a predominant role in treatment of patients with LM. Administration of four anticancer agents—namely, methotrexate (MTX), cytarabine (cytosine arabinoside; Ara-C), liposomal cytarabine (DepoCyt®), and thiotepa (TTP), delivered either alone or in combination via intralumbar and intraventricular routes (via an Ommaya reservoir)—has been evaluated in randomized clinical trials [4]. No one specific regimen demonstrated superior therapeutic efficacy, with the possible exception of DepoCyt® in patients with lymphomatous meningitis. In addition, intrathecal administration of other agents (topotecan, etoposide, and mafosfamide) has been tested in phase II trials, which suggested they had efficacy against LM of solid cancers. The treatment response rates, which were variably assessed, ranged from 20% to 61%, and the median OS varied from 7 to 30.3 weeks. Only one study compared intrathecal and systemic chemotherapy, and it demonstrated that they had comparable efficacy [4].

The toxicity profiles of intrathecal chemotherapy have not been reported uniformly across studies, but serious side effects were noted in 20–86% of patients [4, 17]. The most common complications were radiculitis, bone marrow depression, mucositis, leukoencephalopathy, and chemical arachnoiditis. The combination of intrathecal chemotherapy (in particular, with MTX) and FRT was associated with an increased risk of leukoencephalopathy, which was radiologically diagnosed in all patients 6 months after completion of concurrent therapy [17]. Infectious complications were encountered in 3–18% of cases. Death from treatment-related adverse effects after intrathecal chemotherapy occurred in 4–9% of patients [4, 17].

One of these investigations was a prospective single-arm study of intrathecal MTX combined with dexamethasone, administered concomitantly with involved-field FRT (whole brain radiation therapy (WBRT) and/or spinal canal irradiation) for management of LM of solid cancers in the presence of unfavorable prognostic factors [17]. Overall, 59 patients were enrolled in the trial. Their pretreatment KPS scores ranged from 20 to 70 (median 40), and in 46% of cases, the Glasgow Coma Scale (GCS) score was <15. Bulky CNS disease was present on MRI in 54% of cases. In patients with a KPS score ≤40, induction intrathecal chemotherapy was given initially and the patients were allowed to receive FRT upon neurological improvement. Overall, 51 patients completed concurrent therapy. A clinical response (which was the primary endpoint), assessed according to original clinical criteria (Table 1), was noted in 86.4% of patients. Neurological remission was generally achieved after the first week of treatment. The median OS (which was a secondary endpoint) was 6.5 months (range 0.4–36.7 months), and the 12- and 24-month OS rates were 21.3% and 6.1%, respectively. Twelve patients (20.3%) experienced grade III–V toxicity. The authors concluded that the tested treatment regimen provided significant efficacy, was associated with acceptable morbidity, and might potentially improve QOL in patients who had LM of solid cancers and demonstrated unfavorable prognostic factors [17].

Table 1 Clinical criteria for treatment response assessment in patients with leptomeningeal metastases (according to Pan et al. [17])

Type of response	Neurological symptoms and signs	Karnofsky Performance Scale score
Complete response	Almost normal neurological examination; mild cranial nerve symptoms, including tinnitus or blurred vision, may be present; Glasgow Coma Scale score of 15	Score ≥90
Obvious response	Significant neurological improvement; no severe symptoms/signs such as a severe headache, somnolence, or a decline in mental status; dizziness, confusion, mild headache, cranial nerve palsy, or radiculitis may be present; Glasgow Coma Scale score ≥12	Score ≥70 or increased by ≥30 in comparison with the baseline level
Partial response	Partial neurological improvement; persistent headache or other mild/moderate symptoms/signs; Glasgow Coma Scale score ≥9	Score of 50–70 or increased by 10–20 in comparison with the baseline level
Stable disease	No observable neurological improvement	Score increased by ≤10 in comparison with the baseline level
Progressive disease	Deteriorative neurological symptoms and signs	Score decreased in comparison with the baseline level

The decision regarding the type of response is based on the opinions of at least two experienced neuro-oncologists. The conditions for both neurological symptoms/signs and the Karnofsky Performance Scale score should be satisfied

Nevertheless, the existing level of evidence regarding the efficacy of intrathecal chemotherapy in cases of LM of solid cancers is definitely insufficient. The optimal dosing, schedule of administration, and treatment duration have not been established yet. Of note, after intrathecal administration, anticancer drugs do not penetrate more than 2–3 mm from the CSF–tumor interface [18]. Moreover, beyond MTX, no anticancer drug used for such treatment has demonstrated proven efficacy against adult brain tumors when was given systemically for single-agent therapy [4].

Radiation Therapy

Approximately one third of patients with LM are treated with FRT [18]. It is usually given in cases of bulky lesions and accompanying brain metastases (BM), and it may not only result in their control but also restore CSF circulation, leading to higher efficacy of intrathecal chemotherapy and lowering the risk of its side effects [4, 17]. Moreover, irradiation may augment the therapeutic effects of anticancer agents; thus, both treatment options are frequently used in combination (either sequentially or concurrently) [17, 19].

Craniospinal irradiation for management of LM is controversial. Since the disease is widely disseminated, such treatment has been considered reasonable in selected cases, and regression of neurological symptoms has been noted in more than two thirds of patients during or immediately after the course of therapy [20]. However, related complications are encountered in approximately 30% of cases and may result in significant clinical deterioration, especially in patients who are already in poor medical condition as a result of systemic disease [19]. Prominent myelosuppression, dysphagia, mucositis, and nausea are particularly common. Therefore, because of the high risk of toxicities, involved-field FRT is favored by most clinicians for treatment of patients with LM and is given either as focal irradiation (in 14% of cases) or as WBRT (in 85% of cases) [4, 18, 19].

Few studies have specifically assessed the preventive role of WBRT in development of LM [21]. Jo et al. [22] retrospectively evaluated 827 patients with BM treated with stereotactic radiosurgery (SRS) and reported LM actuarial incidence rates of 3.1% and 5.8% at 6 and 12 months after treatment, respectively. Breast cancer and a large number of intracranial tumors (≥4) were defined as unfavorable risk factors. In comparison with SRS treatment alone, addition of WBRT after radiosurgery significantly decreased the risk of LM [22].

Although WBRT still represents standard treatment of patients with multiple BM and results in improved intracranial tumor control (in particular, distant tumor control), it does not provide a substantial survival benefit and is accompanied by well recognized detrimental effects on cognitive function and QOL [21, 23–26].

Stereotactic Radiosurgery

It is generally considered that there is a limited role for SRS in management of LM. However, occasional application of such treatment in some patients may be rather effective (Fig. 3). Like FRT, radiosurgical targeting of selective lesions may augment the therapeutic efficacy of intrathecal chemotherapy and restore CSF circulation, reducing the risk of side

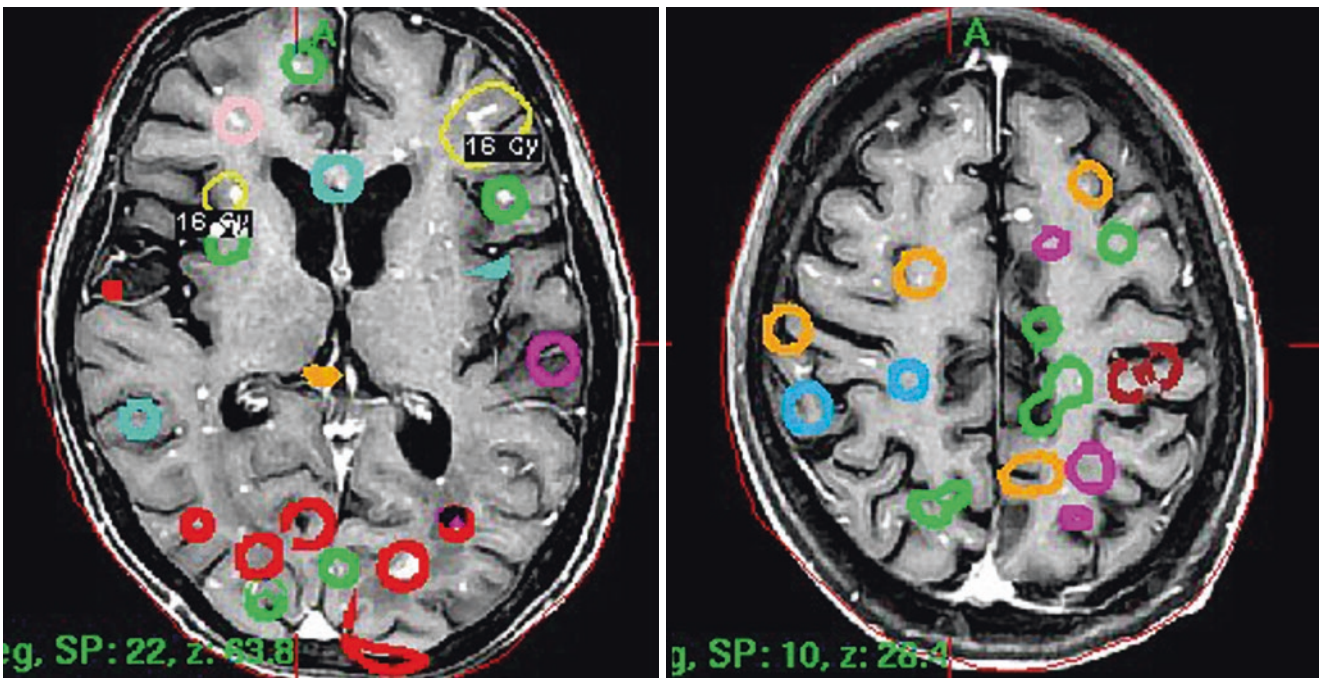

Fig. 3 Postcontrast T1-weighted magnetic resonance imaging in a 38-year-old woman with lung cancer, displayed within Leksell GammaPlan®. The patient underwent eight separate Gamma Knife radiosurgery procedures for nodular metastases within the sulci of the cerebral hemispheres (isocenters used at the time of each treatment are depicted with the different colors). Multiple small parenchymal, subependymal, and sulcal lesions were clearly visible and strongly suggestive of progression of leptomeningeal metastases

effects. In addition, it allows control of bulky BM, which frequently accompanying LM. Such a strategy may decrease the risk of treatment-related complications—in particular, leukoencephalopathy—especially in previously irradiated patients. Nevertheless, the results of combining SRS with other therapies for LM have rarely been reported and largely remain unknown [27, 28].

Meanwhile, postoperative SRS to the resection cavity is frequently considered a possible option for prevention of LM after surgical removal of a BM; however, whether it is really so is still a matter of debate [24, 29–35]. The reported incidence of LM at 5–6 months after surgery followed by postoperative SRS to the resection cavity is 12–17% [29, 32, 34]. Such a high rate might be explained by possible intraoperative spillage of neoplastic cells, resulting in their distant location outside the focal field of irradiation. Johnson et al. [32] evaluated the risk of LM in patients with BM treated with SRS alone ($N = 218$) or with surgical tumor resection followed by SRS to the resection cavity ($N = 112$); the cumulative incidence rates of LM at 12 months after treatment were 5.2% and 16.9%, respectively. In contrast, Huang et al. [31] analyzed 805 patients and found no evidence that resection of BM before SRS increased the risk of LM, which may have reflected the protective effects of irradiation. The main drawbacks of these studies were related to their retrospective design and the prolonged time periods in which treatment was accomplished, resulting in variability in patient selection criteria and different modes of applied adjuvant therapy (including intrathecal chemotherapy and molecular targeted therapy).

A recent multi-institutional randomized controlled phase III trial compared WBRT (with a total dose of 30 Gy delivered in 10 fractions or 37.5 Gy in 15 fractions) with SRS to the resection cavity (the prescription dose varied from 12 to 20 Gy and depended on the target volume, including a 2 mm margin) after surgical removal of BM [36]. The latter regimen provided improved QOL and better preservation of cognitive function, and no significant difference in OS was found between the different treatment arms. Omission of WBRT was accompanied by worse local and distant tumor control, but the incidence of LM at 12 months after treatment did not differ significantly (5.4% versus 7.2%) [36].

As a novel treatment strategy, neoadjuvant SRS has been applied before resection of large BM in an attempt to decrease the risks of intraoperative and postoperative tumor dissemination [37–40]. Its theoretical advantages include clear target definition, the possibility to apply high radiation doses without a risk of adverse events (since the lesion will be resected soon thereafter), and preserved tumor blood flow (i.e., oxygenation) at the time of irradiation, attenuating treatment resistance caused by hypoxia [37]. This may result in effective local control of even voluminous BM (with a largest diameter of >3 cm) and allows avoidance or postponement of postoperative WBRT [37, 38]. In a multi-institutional study, Patel et al. [39] showed that in comparison with SRS to the resection cavity, neoadjuvant SRS before surgery provided comparable local tumor control rates, local and distant recurrence rates, and OS, and this approach was associated with significantly lower incidence of symptomatic radiation necrosis and LM.

Immunotherapy

Blockade of receptors that inhibit the tumor immune response (e.g., cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), or programmed cell death-ligand 1 (PD-L1)) with specific agents (checkpoint inhibitors) is currently being widely tested in various clinical trials. However, the efficacy of such therapy in patients with untreated BM remains unclear, since they are usually excluded from study cohorts.

Nivolumab, a human immunoglobulin G4 anti-PD-1 monoclonal antibody, has been particularly used as second-line therapy for metastatic non–small cell lung cancer (NSCLC) after disease progression in patients receiving platinum-based chemotherapy. Analysis of pooled data from studies on nivolumab presented in 2016 during the annual meeting of the American Society of Clinical Oncology (ASCO) revealed that in patients with CNS metastases, complete or partial responses were noted in 28% of cases, stable disease in 33%, and progressive disease in 39% [41].

Pembrolizumab, a humanized monoclonal antibody against PD-1, has been approved as first- and second-line treatment for metastatic NSCLC. A phase II study on its use in patients with melanoma and NSCLC accompanied with untreated or progressive BM (clinicaltrials.gov identifier NCT02085070) is currently active [42]. Early analysis of its results has revealed an intracranial tumor response rate of 33% in patients with NSCLC, which is comparable to the effects of systemic chemotherapy. However, patients with LM have been excluded from this study [42].

We were able to identify only one report on successful use of ipilimumab against LM in a patient with metastatic melanoma [43]. The disease manifested with a headache, and the diagnosis was confirmed by MRI. WBRT did not lead to a clinical improvement, but subsequent therapy with ipilimumab resulted in resolution of symptoms after the first administration of the agent, accompanied by a complete radiographic response [43].

In addition, intrathecal injection of interferon-α was tested in a phase II study in patients with LM of solid cancers and showed acceptable safety and efficacy profiles [4].

Molecular Targeted Therapy

Recently, there has been growing interest in use of molecular targeted agents for management of LM, and it has been demonstrated that in cases receiving proper dosing and administration regimens, such treatment may be rather effective in appropriately selected patients.

The presence of an epidermal growth factor receptor gene (*EGFR*) mutation and its type in NSCLC are strongly associated with OS, PFS, and a better performance status in patients, even in the presence of LM. In a retrospective study by Umemura et al. [44], administration of tyrosine kinase inhibitors (TKI) targeting EGFR in patients with NSCLC resulted in a median survival time of 3.6 months overall, but it was 11.0 months in individuals with *EGFR* exon 19 deletion, 7.1 months in those with *EGFR* exon 21 mutation, and 1.4 months in those with wild-type *EGFR*. Although there have been no prospective randomized trials on use of anti-EGFR TKI for management of LM, several retrospective studies with historical controls have shown that these therapies may be considered potentially effective options. The problem is that such agents may permeate through the BBB only at low rates; thus, to achieve adequate therapeutic concentrations in CSF, high-dose anti-EGFR TKI treatment was tested in patients with LM of NSCLC. For instance, the BBB permeation rate of erlotinib is approximately 2.8–5.1% [45, 46], but pulsatile high-dose administration of it (1500 mg weekly) results in increased brain concentrations. Nevertheless, most studies have tested such regimens in tumors that progressed in patients receiving a standard-dose first-line anti-EGFR TKI, and no clinical trial evaluating standard-dose versus pulsatile high-dose administration of such an agent has been conducted to date [47]. Another promising treatment strategy for management of LM is combination of an anti-EGFR TKI with WBRT, but the clinical efficacy of this approach also remains unknown.

Amplification of the human epidermal growth factor receptor type 2 gene (*HER2*) typically presents in aggressive forms of cancer (in particular, breast cancer), and molecular targeted therapy in such cases may significantly improve the prognosis. Trastuzumab, a monoclonal antibody targeting HER2, has demonstrated efficacy in HER2-positive breast cancer but has only a limited role in management of LM because of its large molecular size associated with poor BBB permeation [48]. Combination of this agent with FRT may increase its therapeutic efficacy. Stemmler et al. [49] showed that the serum-to-CSF ratios of trastuzumab in patients with BM of breast cancer were 420:1 prior to irradiation and 76:1 after irradiation; moreover, after irradiation in patients with concomitant LM, this ratio was 49:1. Safety and efficacy of intrathecal trastuzumab in cases of HER2-positive breast cancer patients with LM has also been demonstrated [50], but the doses and schedule of such a therapeutic regimen still require clarification.

Treatment Response Assessment

Standardized therapy assessment criteria and algorithms for outcome evaluation in patients with LM have not been established yet, and there is considerable variation in definitions of response according to clinical examination, neuroimaging, and CSF analysis [4]. In particular, the roles of CSF biochemistry, cytology, and tumor markers in monitoring of therapeutic effects and prediction of the prognosis have largely remained unknown. In the series reported by Pan et al. [17], negative CSF cytology after intrathecal chemotherapy was not associated with a better clinical response and prolonged patient survival. On the other hand, in most patients with LM of solid cancers, even clinically effective intrathecal chemotherapy does not result in reduction of leptomeningeal contrast enhancement on MRI [4]. Because of such limitations, treatment response assessments in several studies have been based solely on clinical data, such as changes in patients' neurological status and performance status, and this approach was considered sufficiently appropriate [17].

Personal Experience

In recent years, the authors have usually applied a multimodal treatment strategy in patients with LM of solid cancers. Illustrative cases are presented herein.

Case 1

The details of this case have been reported previously [19]. A 60-year-old man was admitted to our hospital with impairment of consciousness and complaints of a headache and vomiting. MRI disclosed hydrocephalus and signs of LM without any identifiable mass lesion (Fig. 4). Six years earlier, he had been diagnosed with a lung adenocarcinoma (stage IIIB; T4N2M0) and had undergone right upper lobectomy. Three years after that surgery, the tumor had relapsed at the surgical margin; thus, systemic chemotherapy with cisplatin and gemcitabine was given, followed by docetaxel as a second-line treatment. One year later, a distant metastasis in the sacrum was revealed and controlled with FRT (39 Gy in 13 fractions). The patient was also diagnosed with a single BM, which underwent surgical resection.

CSF cytology upon admission revealed adenocarcinoma cells. A ventriculoperitoneal shunt was implanted for management of hydrocephalus. Thereafter, therapy with erlotinib was started concurrently with WBRT (30 Gy in 10 fractions). Craniospinal irradiation was omitted, since the patient was considered unlikely to tolerate it because of his poor general

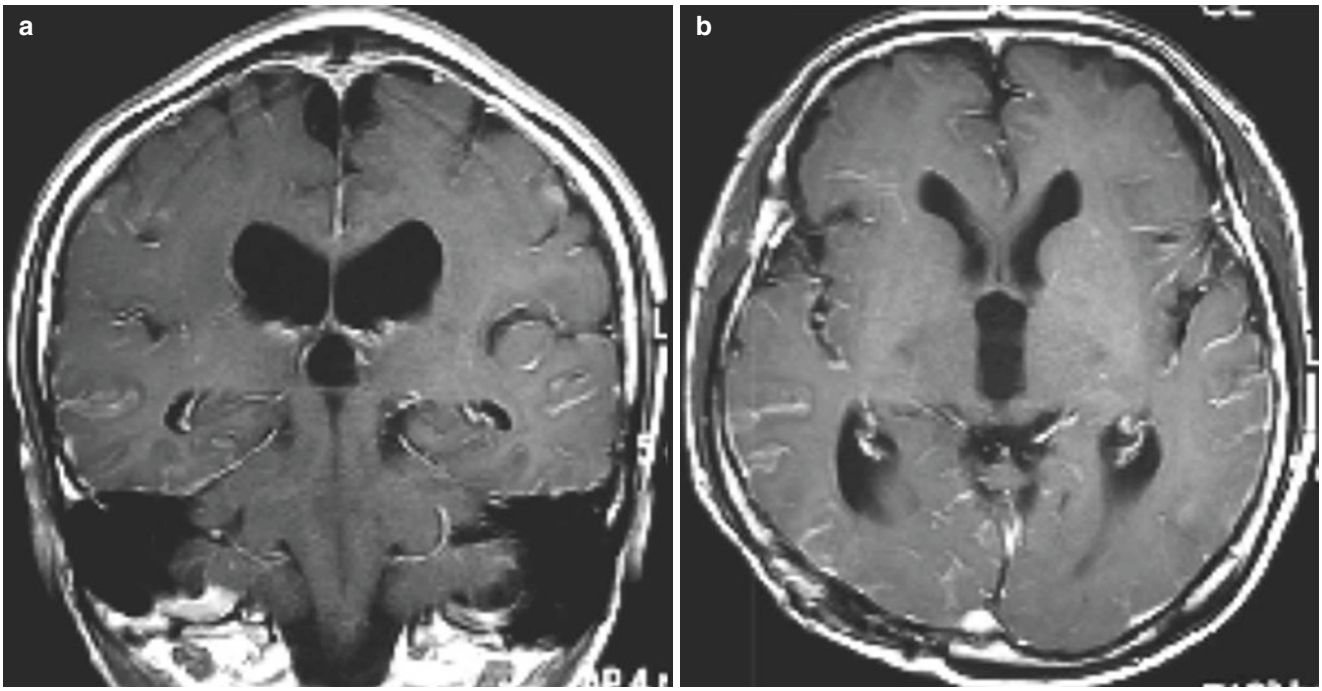

Fig. 4 Postcontrast T1-weighted coronal (**a**) and axial (**b**) magnetic resonance imaging in a 60-year-old man with leptomeningeal metastases of a lung adenocarcinoma (case 1). There was no identifiable mass lesion, but hydrocephalus and bilateral linear enhancement of the cerebral sulci were clearly visible. The diagnosis was confirmed by cerebrospinal fluid cytology, which revealed the presence of neoplastic cells

condition and risk of further deterioration due to possible treatment-related complications. Nevertheless, neurological improvement was noted within a week after initiation of therapy, and control CSF analysis did not disclose any neoplastic cells. The patient survived for 13 months (407 days) after erlotinib treatment had been initiated.

Case 2

A 62-year-old woman was diagnosed with breast cancer and underwent breast-conserving surgery. Pathological examination revealed an invasive ductal carcinoma (stage I; T1cN0M0), which corresponded to the Nottingham histological grade 3 and was negative for estrogen receptor, progesterone receptor, and HER2. The patient was given adjuvant chemotherapy with paclitaxel for 4 months. Eighteen months after her surgery, she started to complain of a headache and dysarthria, and MRI revealed multiple BM located both infra- and supratentorially (Fig. 5a). At the same time, computed tomography (CT) disclosed distant metastases in the lungs, liver, and vertebrae. Gamma Knife surgery (GKS) with a marginal dose of 20 Gy was done twice for control of intracranial tumors (Fig. 5b, c), and systemic therapy with bevacizumab and paclitaxel was given.

However, the patient's pleural effusion increased and new BM were identified; thus, GKS was performed for the third time 3 months after the first radiosurgical treatment. At that time, MRI demonstrated enlarged ventricles and linear contrast enhancement of cerebral sulci, indicating LM (Fig. 5d–f). All previously irradiated BM had either disappeared or shrunk. The largest lesion identified on the initial MRI, which had a diameter of 28 mm and was located superficially in the right cerebellar hemisphere, was suspected to be a source of leptomeningeal dissemination. A ventriculoperitoneal shunt was implanted for management of hydrocephalus, but the patient died of systemic disease progression 2 months later.

Case 3

A 75-year-old man was diagnosed with squamous cell lung cancer (stage IIB; T2bN1M0). At that time, postcontrast brain MRI did not demonstrate specific findings. The patient underwent right upper lobectomy and systematic lymphadenectomy, followed by four cycles of adjuvant chemotherapy with docetaxel and carboplatin. A routine follow-up examination 12 months after surgery incidentally revealed a single BM located in the left occipital lobe, with a diameter of 37 mm. The patient was neurologically intact. No extra-

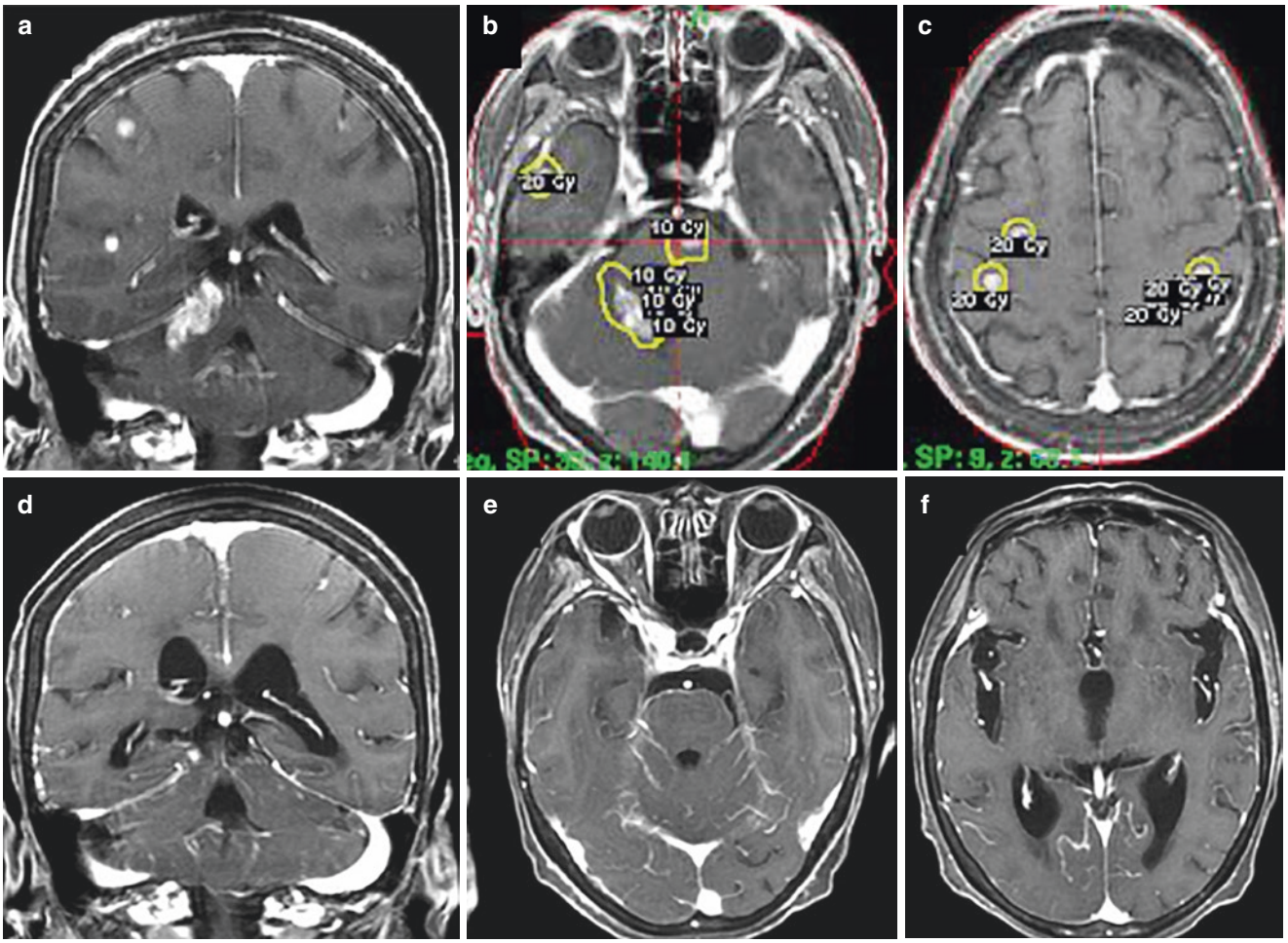

Fig. 5 Postcontrast T1-weighted magnetic resonance imaging (MRI) in a 62-year-old woman with breast cancer (case 2). The initial examination 18 months after breast-conserving surgery revealed multiple brain metastases located both infratentorially and supratentorially (**a**), which were controlled with two Gamma Knife radiosurgery procedures (**b**, **c**). However, 3 months after the first radiosurgical treatment, MRI demonstrated new brain lesions, hydrocephalus, and linear contrast enhancement of the cerebral sulci (**d**–**f**), indicating leptomeningeal metastases. All previously irradiated brain tumors had either disappeared or shrunk

cranial metastases were disclosed. Three-stage GKS was performed with a total marginal dose of 30 Gy (10 Gy per stage) (Fig. 6a). The tumor was stable during 7 months of subsequent follow-up but showed regrowth thereafter; thus, it was removed surgically (Fig. 6b). This was followed by SRS to the resection cavity, performed in the early postoperative period. Nevertheless, a second recurrence was noted 3 months later, and reresection of the lesion was performed (Fig. 6c, d).

Despite the decrease in the tumor burden, 3 months after recraniotomy (13 months after the first SRS), an extensive LM mainly affecting the left cerebral hemisphere were disclosed (Fig. 6e). The patient died 2 months later, a total of 15 months after the single BM had been diagnosed.

Case 4

A 57-year-old woman was diagnosed with lung adenocarcinoma harboring an *EGFR* mutation. Right upper lobectomy was performed. Adjuvant therapy was omitted. One year after surgery, multiple BM were incidentally found during a routine follow-up examination. There were no neurological symptoms. At that time, chest CT did not reveal recurrence of the primary cancer. The patient underwent GKS for ten brain lesions (with a marginal dose of 24 Gy delivered at prescription isodose line of 70%) (Fig. 7a, b), and she was followed up thereafter with MRI without additional adjuvant therapy. WBRT was omitted to avoid possible cognitive and neurological declines that might affect her professional abilities, as their preservation was of paramount importance to

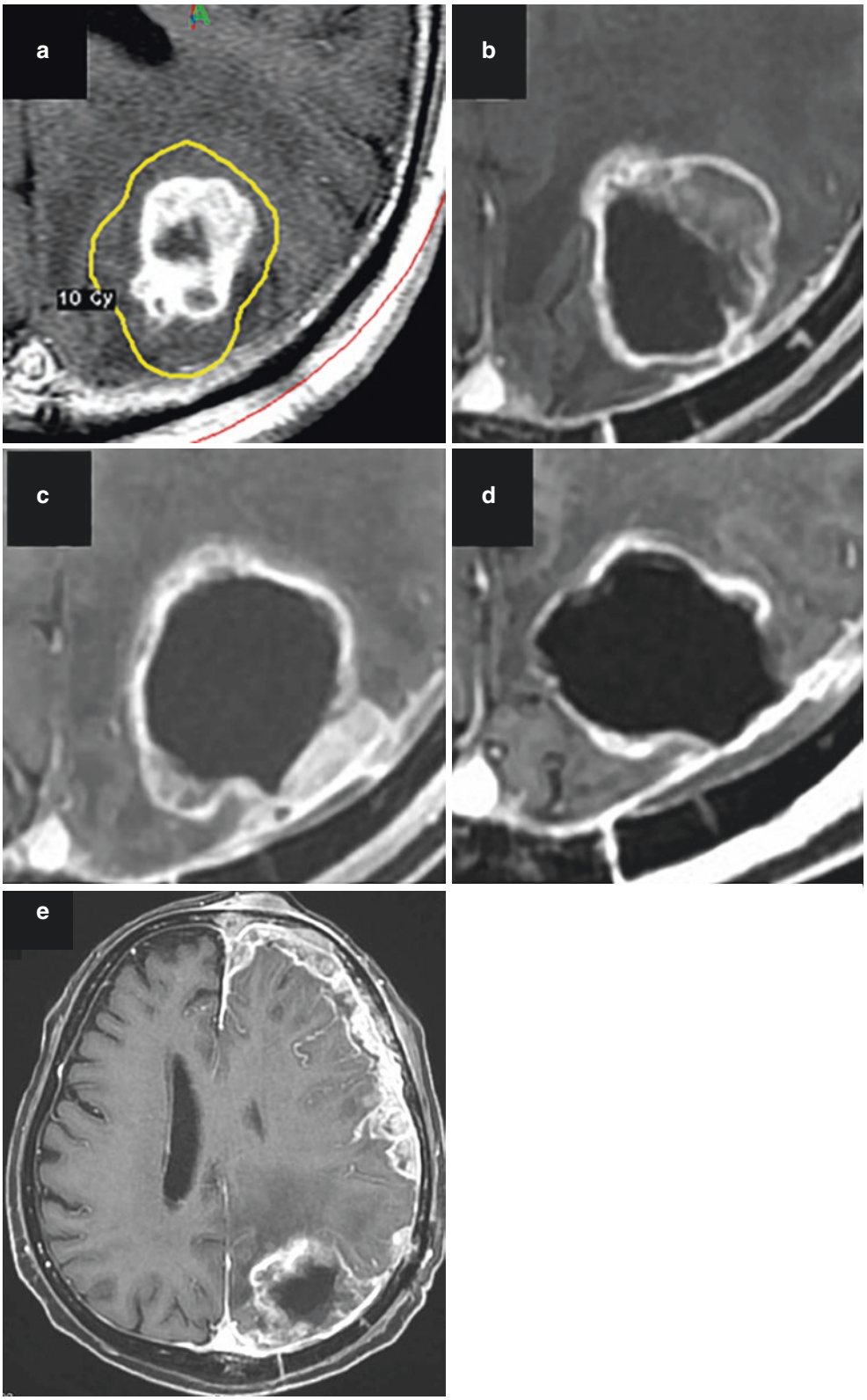

Fig. 6 Postcontrast T1-weighted magnetic resonance imaging in a 75-year-old man with lung cancer (case 3). The initial examination during routine follow-up 12 months after upper lobectomy and systematic lymphadenectomy revealed a single asymptomatic brain metastasis (with a maximum diameter of 37 mm) in the left occipital lobe, and three-stage Gamma Knife radiosurgery with a total marginal dose of 30 Gy (10 Gy per stage) was performed (**a**). After the tumor had been controlled for 7 months, its regrowth was noted, and surgical removal of the lesion was performed (**b**), followed by postoperative radiosurgery to the resection cavity. Nevertheless, a second recurrence was diagnosed 3 months later (**c**), and reresection of the lesion was performed (**d**). Despite the decrease in the tumor burden, massive leptomeningeal metastases, mainly affecting the left cerebral hemisphere, were found 3 months after recraniotomy (**e**)

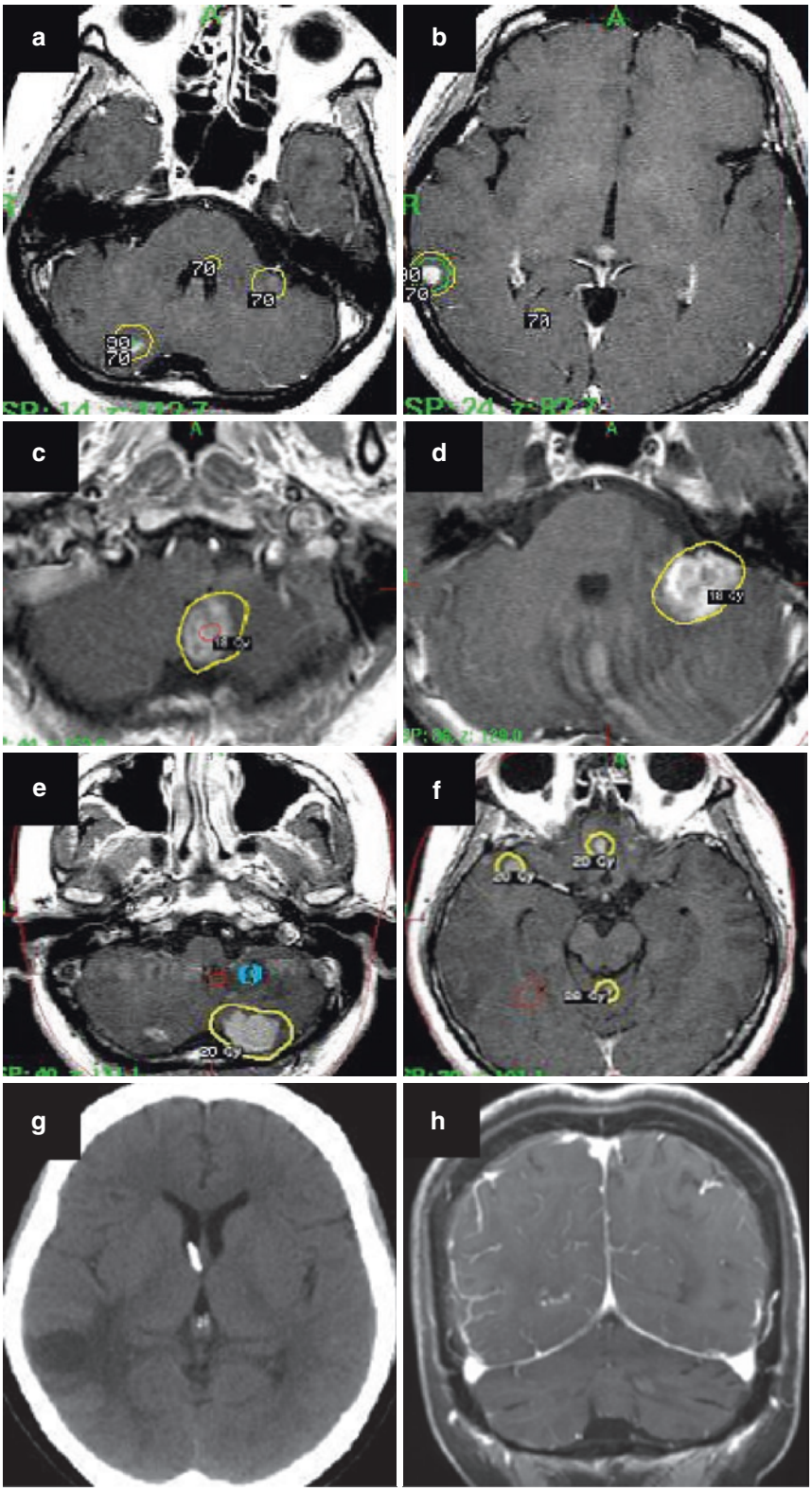

Fig. 7 Brain imaging findings in a 57-year-old woman with a lung adenocarcinoma (case 4), who underwent Gamma Knife surgery (GKS) three times for management of intracranial metastases, followed by intrathecal chemotherapy. The first GKS was performed 12 months after resection of the primary cancer for ten tumors located both infratentorially (**a**) and supratentorially (**b**). Whole-brain radiation therapy was omitted. After 43 months of follow-up, the second GKS was performed for newly diagnosed tumors in the vermis (**c**) and in the left cerebellar hemisphere (**d**). The third GKS was performed 12 months later for six newly diagnosed tumors, located both infratentorially (**e**) and supratentorially (**f**), soon after implantation of an Ommaya reservoir (**g**). Despite intrathecal chemotherapy combined with systemic chemotherapy and molecular targeted therapy for 14 months, the patient developed radiological signs of leptomeningeal metastases (**h**) and died of her disease

the patient. Indeed, during the subsequent observation period, she maintained good performance, did not demonstrate neurological symptoms, and worked as a teacher of mathematics at a high school.

At 43 months of follow-up, two new BM were found in the vermis and the left cerebellar hemisphere, and these were treated with GKS again (with a marginal dose of 20 Gy delivered at prescription isodose line of 60%) (Fig. 7c, d). Eleven months after the second GKS, follow-up MRI demonstrated six new metastases, predominantly located on the surface of the cerebellar and cerebral cortices. Cytological examination of CSF revealed a CEA level of 19.5 ng/mL. An Ommaya reservoir was implanted, and intrathecal chemotherapy with MTX and Ara-C was initiated. At the same time, a third GKS was performed for newly revealed BM (Fig. 7e–g). Although positron emission tomography (PET)–CT did not demonstrate either recurrence of the primary cancer or somatic metastases, systemic chemotherapy combined with molecular targeted therapy was initiated (a combination of nab-paclitaxel, gemcitabine, carboplatin, and bevacizumab for 2 weeks, followed by pemetrexed, gemcitabine, carboplatin, and bevacizumab for 4 months, with subsequent administration of afatinib for 8 months).

The patient was in a stable condition and did not demonstrate neurological deterioration or MRI findings suggestive of LM. During administration of the anticancer therapies, she continued her teaching work. However, 14 months later, she developed an episode of headache and nausea. Her CEA levels were elevated in both serum and CSF. MRI demonstrated hydrocephalus and LM (Fig. 7h). Rechallenge systemic chemotherapy combined with molecular targeted therapy for 3 months was not effective, and the patient was transferred for palliative and supportive care. She died of her disease 27 months after intrathecal chemotherapy had been initiated.

Conclusion

The existing therapeutic options for LM of solid cancers are limited, and outcomes in such cases generally remain unsatisfactory, with poor understanding of associated prognostic and predictive factors. Conventional treatment with intrathecal chemotherapy with or without involved-field FRT has only modest efficacy; thus, there is a definite need for development of new, more aggressive multimodal therapeutic strategies, particularly for patients with controlled systemic disease. Immune checkpoint inhibitors and other molecular targeted therapies have demonstrated promising results and may potentially be used either in combination with, or even as an alternative to, WBRT in selected groups of patients. There may be an important role for SRS as well, since it allows effective control of bulky intracranial lesions, reduces the risk of tumor dissemination after surgical resection, and decreases the rate of radiation-induced complications. Because organization of prospective randomized multi-institutional trials on treatment of LM of solid cancers may be problematic, practical guidelines for optimal therapeutic strategies in such cases should be established on the basis of integrated and critically analyzed results of small-scale prospective and retrospective studies.

Conflict of Interest The authors have no conflict of interest concerning the reported materials or methods.

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Stereotactic Radiosurgery to Prevent Local Recurrence of Brain Metastasis After Surgery: Neoadjuvant Versus Adjuvant

Ian E. McCutcheon

Abstract Over the past 15–20 years, stereotactic radiosurgery (SRS) has become the dominant method for treating patients with brain metastases (BM). The role of surgery for management of large tumors also remains important. Combining these two treatment modalities may well achieve the best local control, safety, and symptomatic relief in cases of neoplasms for which resection is desirable. After 10 years of retrospective studies that suggested patients might do better if surgery were followed by early adjuvant SRS, a prospective, randomized, controlled trial was conducted to compare such treatment with postoperative observation after tumor removal, and it showed significantly better local control in the former cohort, especially in smaller lesions, but no difference in overall survival. On the other hand, in the past 5 years, some groups have argued that neoadjuvant SRS before resection of BM might be superior to adjuvant SRS, while no clinical trial has yet been concluded that compares these two treatment strategies. For now, adjuvant and neoadjuvant SRS show evidence of utility in achieving better local control after surgical removal of BM in comparison with surgery alone, but no specific guidelines exist favoring one method over the other, and both should be considered beneficial in clinical care.

Keywords Adjuvant radiosurgery · Intracranial metastases Neoadjuvant radiosurgery · Recurrence · Resection cavity Stereotactic radiosurgery · Surgery

Introduction

The treatment of brain metastases (BM) has evolved from nihilism to fractionated whole-brain radiation therapy (WBRT) to surgery combined with WBRT to single-session stereotactic radiosurgery (SRS). Over the past 15–20 years, concerns over the neurocognitive effects of WBRT and over its limited efficacy against relatively radioresistant tumors have made SRS the dominant method used for managing BM. The role of surgery, however, remains important, as many such neoplasms either are too large for SRS, exert a worrisome mass effect, or provoke edema and symptoms best dealt with by resection. This dual methodology has given rise to the notion that combining SRS with surgery may well achieve the best local tumor control, safety, and symptomatic relief in patients with that subset of BM for which operative intervention is desirable. The clinical results and technical nuances of performing surgical resection combined with either adjuvant or neoadjuvant SRS are reviewed herein in order to clarify their respective utility and safety, and to analyze the relative merits and demerits of each approach.

Controlling Brain Metastases with Surgery and Whole-Brain Radiation Therapy

Surgical resection of BM is well established as an effective way of mitigating the negative effects of such tumors on both overall survival (OS) and the neurological function of patients. Proof of its efficacy comes from two randomized clinical trials performed in the 1990s, both done in cases of a single brain lesion [1, 2]. The earlier trial addressed whether results from surgery followed by WBRT were superior to those from WBRT alone [1]. It showed longer OS (median 40 versus 15 weeks; $P < 0.01$), a lower risk of local tumor recurrence (20% versus 52%; $P < 0.02$), and a longer interval of maintenance of good functional status (median 38 versus 8 weeks; $P < 0.005$) in the surgical group [1]. The later trial, done in Europe, confirmed these results [2]. WBRT administered as an adjuvant to surgery was for many years standard practice based on a third randomized trial, again addressing only patients with a single brain lesion; the incidence of local

I. E. McCutcheon (✉)
Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: imccutch@mdanderson.org

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*, Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_9,

recurrence was significantly higher (70%) with surgery alone than with adjuvant WBRT (18%) [3]. In these early studies, the completeness of tumor removal was not quantified and en bloc resection was not generally done. A more recent study showed that even after radiographically proven gross total resection (GTR) of BM, the incidence of local recurrence was 42% [4].

The majority of patients with BM do not, however, harbor a single tumor. Although no randomized trial to date has addressed the relative utility of surgery and radiotherapy in cases of multiple BM, Bindal et al. [5] retrospectively showed that patients from whom all radiographically evident intracranial tumors had been removed fared better than did those with more than one lesion left unresected. Both OS (median 14 versus 6 months; $P = 0.003$) and functional improvement (83% versus 65%; $P = 0.09$) were more favorable in those individuals who underwent removal of all neoplasms [5]. We tend now to limit craniotomy for BM to those patients who need relief of neurological symptoms caused by a mass effect or who need reduction of increased intracranial pressure caused by tumor-associated cerebral edema refractory to steroid therapy and/or hydrocephalus. When multiple BM are present, we tend to remove the dominant tumor when it is symptomatic or endangering neurological function; additional neoplasms are removed if they sit within the same craniotomy opening. If more than one BM is dominant, a second concurrent craniotomy is performed to remove that tumor as well.

Stereotactic Radiosurgery

The limitations of resection include its invasive nature and the risks that surgical manipulations pose to functional cortex and white matter tracts adjacent to the tumor margin. Because the probability of neurological decline can be significant if the neoplasm is located in eloquent brain region, and since local recurrence and leptomeningeal dissemination after surgery are still possible even when en bloc resection is attained, treatment strategies have shifted from a predominant tendency to use surgery in the 1990s and early 2000s to SRS as the main therapeutic method in patients with BM, both single and multiple [6, 7].

WBRT is not as effective as SRS at securing local tumor control, and it is associated with neurotoxicity leading to neurocognitive decline, particularly in those individuals who survive past the first year [8, 9]. It was specifically demonstrated in a randomized trial by Chang et al. [10], who evaluated patients with 1–3 newly diagnosed BM. WBRT did significantly reduce local tumor recurrence after SRS; however, patients receiving both WBRT and SRS were more likely (52%) to suffer a decline in memory and cognition than were those who had SRS alone (24%) [10]. These results were confirmed by a more recent, multicenter, randomized trial by Brown et al. [11], who found that cognitive deterioration–free survival was significantly longer following adjuvant SRS than following adjuvant WBRT after initial surgical resection. Since OS was similar in the two groups, the authors recommended using SRS for controlling BM because of its lower risk of imposed neurotoxicity [11].

SRS is effective in patients with a limited number of BM and works best in smaller tumors (i.e., those with a maximum diameter <3 cm) [12]. Patients with larger neoplasms or those with a dominant BM causing a mass effect, neurological decline, and/or intractable edema still need surgery. In addition, some individuals will choose tumor removal over SRS. The main problem is this: even in the hands of an experienced and careful neurosurgeon, incomplete removal occurs in at least 15% of cases. Greater success is achieved with en bloc resection, but not all tumors can feasibly be resected in such a way (Fig. 1). Given that both surgery and SRS are established as effective ways to treat patients with BM, a number of neurosurgical oncologists have suggested combining both modalities. How best to combine them—whether it is safer and more effective to use SRS in a neoadjuvant fashion before surgery or after surgery as an adjuvant treatment—is a matter of current debate. As the evidence on the effectiveness of neoadjuvant SRS is retrospective and nonrandomized, but two prospective, randomized trials have been done with adjuvant SRS, the latter will be discussed first.

Adjuvant Radiosurgery

With the excellent local control of BM attained by SRS and the advantages offered by surgery for selected patients, starting from the 2000s some groups began to apply single-session SRS to the postoperative cavity after removal of one or more metastases [13–43]. These initial clinical series varied widely in terms of the type of patients included, the SRS device used, the interval between surgery and SRS delivery, the mix of tumor histologies, and the degree of resection done prior to irradiation (Table 1). The utility of these, mostly retrospective, analyses derives more from their advancing the feasibility of the idea than from their establishing the likelihoods of local tumor control or of complications after sequential combination of the two treatment modalities. Although reported results have suggested 1-year local tumor control rates of 70–90% with adjuvant SRS overall, such data can be derived in an unbiased way only from randomized, controlled trials.

Nonetheless, it is of interest to sample from these published retrospective studies. In one representative series, Jensen et al. [26] reported the results of using SRS to treat

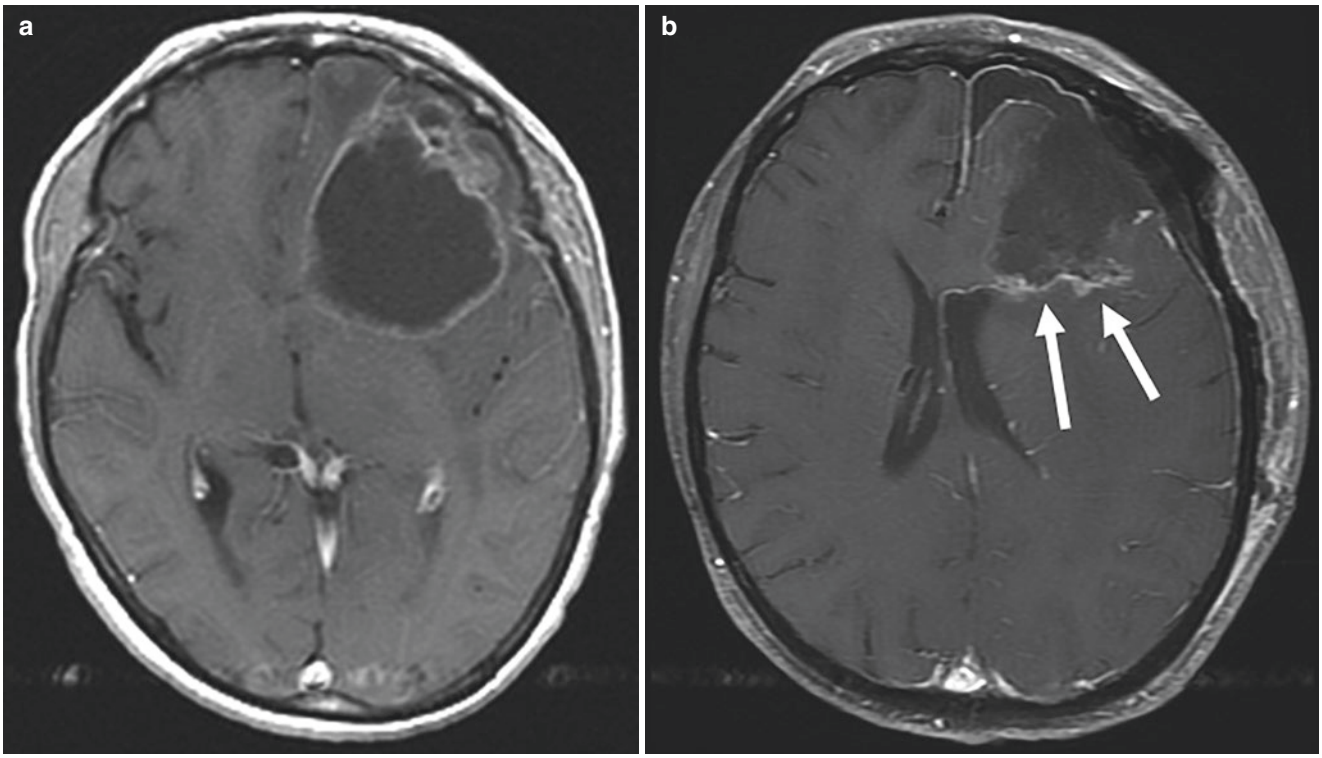


Fig. 1 Postcontrast T1-weighted magnetic resonance imaging before (**a**) and after (**b**) surgery demonstrates a large cystic brain metastasis of a non–small cell lung carcinoma causing a midline shift, a mass effect, and peritumoral edema. The patient presented with cognitive deficits and expressive dysphasia. This lesion is too large and too soft to remove it en bloc, and the cyst content must be drained early in a procedure for safety. Thus, piecemeal tumor removal is done. After surgery, the mass effect is relieved, but a small area at the posterior margin of the resection cavity (*arrows*) shows contrast enhancement suggestive of a residual neoplasm. This patient needs adjuvant stereotactic radiosurgery to enhance local control at the operative site

112 resection cavities in 106 patients who had undergone removal of BM (achieving GTR in 96% of cases, which is excellent). In their practice, WBRT was not used routinely. The median interval from surgery to SRS was 24 days. A local tumor control rate of 80% was noted, with median post-treatment OS of 10.9 months. Multivariate analysis showed that patients with irradiated resection cavities ≥3 cm in diameter had a 13-fold excess risk of recurrence in comparison with those with smaller resection cavity volumes [26]. This is reasonable, as the greater marginal surface area of a larger cavity is more likely not only to harbor radiographically occult residual tumor tissue but also to contain spatial irregularities that make it harder to do selective irradiation without including adjacent brain tissue.

The series by Kim et al. [31] addressed the particular issue of adjuvant SRS after surgical salvage following failure of prior WBRT. This group had an excellent rate of GTR (95%) and achieved a 95% local tumor control rate at 1 year after SRS, with only 3.8% of patients showing subsequent radiation necrosis [31]. By contrast, Roberge et al. [41] gave SRS before, during, or shortly after WBRT and noted a comparable rate of radiation necrosis (5%) in their cohort. These data suggest that prior or planned subsequent exposure to WBRT should not disqualify patients from undergoing SRS as a means of potentiating the positive effects of salvage surgery.

Brennan et al. [16] reported the first patient cohort of adjuvant SRS collected prospectively. Irradiation was given from 2 to 8 weeks after surgery. The doses delivered were dependent on the resection cavity volume, with 15 Gy used for cavities with a maximum diameter of 3.1–4.0 cm, 18 Gy for those measuring 2.1–3.0 cm, and 22 Gy for those measuring ≤2.0 cm. Eleven of the 50 enrolled patients were excluded from the final analysis because of early progression of local or distant disease; thus, 39 operated individuals underwent SRS in 40 resection cavities. The median post-treatment OS was 14.7 months. Local tumor recurrence was seen in 15% of the irradiated patients and in 50% of those who had been enrolled but had not undergone SRS. These may, of course, not have been truly comparable groups; since individuals excluded from adjuvant SRS had shown early recurrence, their tumor biology may have been different from that in patients within the treatment cohort. The authors noted that superficially located neoplasms of a large size (≥3 cm) had the highest risk of local treatment failure [16]. Hartford et al. [21] have also reported a higher inci-

Table 1 Summary of retrospective studies on the results of stereotactic radiosurgery (SRS) to the resection cavity after surgical removal of brain metastases (BM)

Study	Institution	SRS device used for treatment	Number of patients	Number of BM resection cavities treated	Proportion of cases with a single BM (%)	Proportion of cases with complete resection of BM (%)	Median interval between surgery and SRS (days)	Proportion of cases with WBRT (%)	Median survival time (months)	1-Year local recurrence rate (%)	1-Year distant brain failure rate (%)	Symptomatic radiation necrosis rate (%)	Leptomeningeal dissemination rate (%)
Bahl et al. (2006) [15]	University of California San Diego	LINAC	7[a]	7	100	ND	68	ND	ND[b]	ND[b]	ND[b]	ND	ND
Kim et al. (2006) [31]	Wake Forest University	GK	79	ND	ND	ND	ND	100	17	5	ND	3.8	5.1
Iwai et al. (2008) [24]	Osaka City General Hospital	GK	21	21	76	100	ND	ND	20	18	48	ND	24
Mathieu et al. (2008) [34]	Sherbrooke University; University of Pittsburgh	GK	40	40	68	80	28	16	13	26	54	0	ND
Quigley et al. (2008) [39]	Allegheny General Hospital	LINAC	32	46	65	ND	35	28	20	ND	ND	0	ND
Soltys et al. (2008) [44]	Stanford University	CK	72	76	65	85	ND	19	15.1	21	47	4	ND
Do et al. (2009) [19]	University of California Irvine	LINAC/TT[c]	30	33	43	ND	ND	47	12	18	ND	5	ND
Jagannathan et al. (2009) [25]	University of Virginia	GK	47	47	28	100	15	28	11	ND	ND	ND	ND
Karlovits et al. (2009) [28]	Allegheny General Hospital	LINAC	52	52	65	92	41	31	15	ND	60	0	ND
Limbrick et al. (2009) [32]	Washington University	GK	15	16	80	81	ND	40	20	27	60	ND	ND
Roberge et al. (2009) [41]	McGill University	LINAC/CK	38	38	100	95	43	100	17.6	6	6	5	ND
Hwang et al. (2010) [22]	Tufts Medical Center	GK	25	25	ND	95	ND	ND	15	0	33	ND	ND

Kalani et al. (2010) [27]	Barrow Neurological Institute	GK	68	68	ND	100	16	ND	13.2	ND	ND	ND	ND
Jensen et al. (2011) [26]	Wake Forest University	GK	106	112	58	96	24	37	10.9	13	54	2.8	7.5
Rwigema et al. (2011) [42]	University of Pittsburgh	CK[c]	77	89	86	100	34	26	14.5	24	47	2.6	ND
Choi et al. (2012) [17]	Stanford University	CK[c]	112	120	63	90	21	28	17	9	59	7	ND
Kelly et al. (2012) [30]	Dana-Farber Cancer Institute	LINAC (frameless)[c]	17	18	ND	94	ND	24	ND	ND	35	0	ND
Ogiwara et al. (2012) [35]	Northwestern University	GK	56	56	100	100	19	14	21	ND	38	ND	ND
Prabhu et al. (2012) [37]	Emory University	LINAC[c]	62	64	71	81	31	ND	13	22	ND	8	ND
Robbins et al. (2012) [40]	Henry Ford Hospital	LINAC	85	85	62	68	18	35	12	19	55	8	8.2
Atalar et al. (2013) [14]	Stanford University	CK	165	175	ND	91	ND	ND	17	10	54	ND	13
Hartford et al. (2013) [21]	Dartmouth College	LINAC	47	49	70	76	23	45	ND	14	63	ND	ND
Kellogg et al. (2013) [29]	Rush University	LINAC[c]	59	59	ND	ND	26	42	15.3	2	ND	ND	ND
Luther et al. (2013) [33]	University of Pittsburgh	GK	120	120	ND	100	ND	39	ND	17	40	3	ND
Brennan et al. (2014) [16]	Cornell University	LINAC	39	40	ND	92	ND	ND	14.7	22	47	17.5	ND

(continued)

Table 1 (continued)

Study	Institution	SRS device used for treatment	Number of patients	Number of BM resection cavities treated	Proportion of cases with a single BM (%)	Proportion of cases with complete resection of BM (%)	Median interval between surgery and SRS (days)	Proportion of cases with WBRT (%)	Median survival time (months)	1-Year local recurrence rate (%)	1-Year distant brain failure rate (%)	Symptomatic radiation necrosis rate (%)	Leptomeningeal dissemination rate (%)
Iorio-Morin et al. (2014) [23]	Sherbrooke University	GK	110	113	ND	81	21	ND	11	27	ND	6	11
Ojerholm et al. (2014) [36]	University of Pennsylvania	GK	91	96	ND	82	42	33	22.3	19	64	6	14
Abel et al. (2015) [13]	University of Southern California	GK	85	ND	ND	54	25	ND	ND	14	53	8	ND
Choi et al. (2015) [18]	Sungkyunkwan University	GK	24	25	ND	ND	14.5	0	11	29	ND	0	ND
Prabhu et al. (2017) [38]	Emory University; Levine Cancer Institute	LINAC	94	ND	68	100	ND	ND	ND	19	ND	23	16
Foreman et al. (2018) [20]	University of Alabama	GK/LINAC	91	91	70	ND	ND	ND	ND	16	ND	5.5	35

CK CyberKnife, *GK* Gamma Knife, *LINAC* linear accelerator, *ND* no data, *TT* tomotherapy, *WBRT* whole-brain radiation therapy

[a]Only two patients were treated with SRS; the others received hypofractionated stereotactic radiotherapy

[b]Not calculated, because the number of patients was insufficient

[c]A few patients were treated with a hypofractionation regimen

dence of (and shorter time to) both local and distant recurrence in larger tumors after adjuvant SRS. This is logical, given the larger surface area of the resection cavities being treated. Patients with non–small cell lung carcinoma (NSCLC) showed a lower risk of local failure than patients with BM of other histologies (14% versus 32% at 12-month follow-up; $P = 0.048$), and the distant brain failure rate was 44% [16], which is comparable to that seen in other series [17, 26]. The incidence of radiation necrosis after SRS was 17.5%, with none of the patients so affected coming from the group getting the highest dose [16]. This rate exceeds the 3–4% range reported in other series, but it may have been caused by unmeasured variables such as use of adjuvant or neoadjuvant chemotherapies [17, 26, 44].

Prospective, Randomized Trials

Two prospective trials addressing adjuvant SRS after surgical removal of BM were published in the same issue of *Lancet Oncology* in August 2017 [11, 45]. One of these studies, by Brown et al. [11], compared a multicenter cohort of patients who received postresection adjuvant SRS ($N = 98$) with a second cohort treated with adjuvant WBRT ($N = 96$). Those with subtotally resected tumors were not excluded from the analysis. The primary outcome measures were OS and cognitive deterioration–free survival. The significant advantage that adjuvant SRS gave patients regarding maintenance of cognitive performance has already been alluded to above, as has the relatively equal OS in the two groups. The risk of new hearing impairment was also higher after WBRT. Although local and regional tumor control was not a primary endpoint, it was assessed; despite the equivalence in OS, SRS was associated with a shorter time to both local and distant brain failure, and each of these differences was statistically significant [11]. This study shows that if adjuvant radiation treatment is desired after surgery for BM, the preferred choice is SRS because it maintains quality of life (QOL) better than does WBRT, without causing a difference in OS.

In a companion trial, Mahajan et al. [45] compared adjuvant SRS with postoperative observation after GTR of BM in a cohort of patients treated at the MD Anderson Cancer Center. In all cases, between one and three intracranial tumors were identified prior to surgery. All patients underwent radiologically complete resection of at least one BM—a requirement more attainable in a single institution with a consistent surgical philosophy among its surgeons. Thus, adjuvant SRS was considered only after GTR of the tumor. The maximum resection cavity diameter allowed for inclusion in the study was 4 cm. The other main exclusion criteria comprised a Karnofsky Performance Scale (KPS) score <70, evidence of leptomeningeal dissemination, and prior WBRT, SRS, or surgical removal of any BM. Randomization and radiation treatment were accomplished within 30 days of surgery (Fig. 2). In the SRS group, the target volume included the entire resection cavity plus a

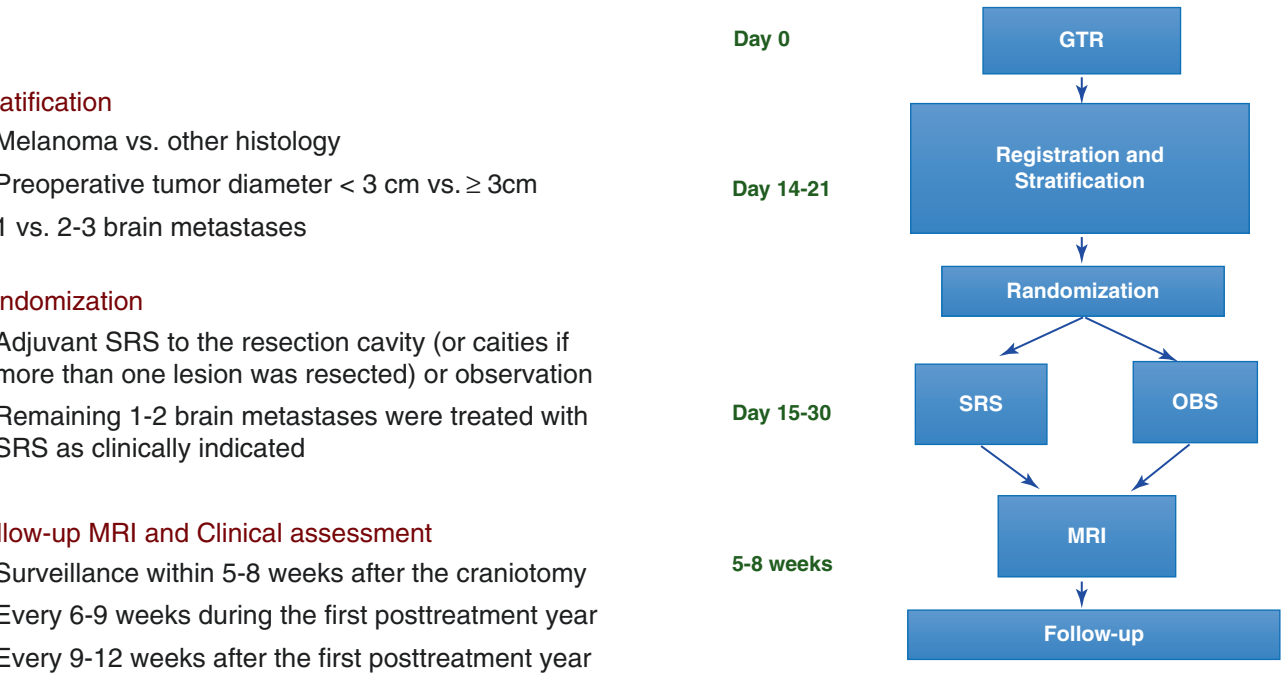


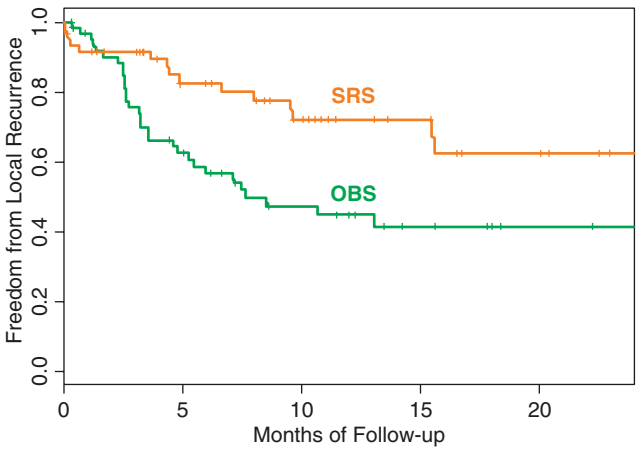
Fig. 2 General structure of a prospective, randomized, controlled trial of adjuvant stereotactic radiosurgery (SRS) versus observation (OBS) after gross total resection (GTR) of brain metastases [45]

margin of 1 mm, as determined from magnetic resonance imaging (MRI) done on the day of treatment. The prescribed doses were 16, 14, and 12 Gy for cavity volumes of ≤10, 10.1–15, or >15 cc, respectively. Distant BM were managed at the physician's discretion. Patients remained in the study until local treatment failure or administration of WBRT, but they were followed up after those events to record OS. Local failure was defined as any recurrence seen on follow-up MRI within the surgical cavity. When more than one lesion had been resected (and thus more than one cavity was treated with SRS or observed), treatment failure in any cavity was considered as an "event." Ambiguous MRI findings that were eventually found to be local treatment failures were censored at the first date of their initial detection. The evaluated baseline characteristics included sex, race, age, primary cancer type, systemic disease status, Graded Prognostic Assessment (GPA) score, number and size of treated BM, and en bloc versus piecemeal tumor resection. After application of the exclusion criteria, the demographic profiles of the observation group ($N = 65$) and the treatment group ($N = 63$) were equivalent. The numbers of patients actually randomized ($N = 132$) and included in the study ($N = 128$) yielded approximately 80% power to detect differences based on a hazard ratio (HR) of 0.596.

This trial showed that SRS to the resection cavity after removal of one, two, or three BM did significantly improve local tumor control in comparison with surgery followed by observation. During a median follow-up period of 11.1 months, the 1-year freedom from local recurrence rates were 72% in the SRS group but only 43% in the observation group ($P = 0.015$) (Fig. 3). There was no significant difference in the incidence of local recurrence with regard to the number of resection cavities treated, method of tumor removal, GPA score, or tumor histology (melanoma versus others); however, recurrence was more likely in patients with larger tumors (maximum diameter ≥2.5 cm). Neither OS nor freedom from distant brain failure differed between the treatment and observation groups [45]. Taken in conjunction with the results from work by Brown et al. [11], this level I evidence strongly suggests that surgical removal of BM followed by adjuvant SRS is superior to surgery alone on the grounds of efficacy and is superior to surgery followed by adjuvant WBRT on the grounds of better preservation of cognition.

Technical Nuances of Target Contouring

Contouring of the clinical target volume (CTV) of a resection cavity rather than an intact BM is operator dependent. In an attempt to develop some standard practices for treatment planning and radiation dosimetry during adjuvant SRS, Soliman et al. [43] published a consensus statement by ten experts drawn from radiation oncology and neurosurgical oncology. A high degree of agreement was found among the contouring plans created by them for ten representative cases of resected BM. From analysis of those plans and from surveys submitted by the participants, a set of recommendations was made. In particular, it was emphasized that the CTV should include not only the entire contrast-enhancing rim of the surgical cavity but also the entire surgical tract used to gain access to the tumor; if the tumor touched the dura, the CTV should include a 5 to 10 mm margin along the cranium beyond the area of preoperative tumor contact; if the tumor did not touch the dura, the CTV should extend 1–5 mm along the cranium, away from the edges of the surgical corridor; and if the tumor touched a venous sinus, the CTV should include a 1 to 5 mm margin along the sinus wall from the point of contact [43]. However, these guidelines did not men-



Arm	Local control rate		Hazard Ratio
	At 6 months	At 12 months	
OBS	57%	43%	0.46 (95% CI: 0.24-0.88) P = 0.015
SRS	83%	72%	

Arm	Median time to local recurrence	95% CI
OBS	7.6 months (30 weeks)	5.3 months – not reached
SRS	Not reached	15.6 months – not reached

Fig. 3 Summary of the main results of a prospective, randomized, controlled trial of postoperative stereotactic radiosurgery (SRS) versus observation (OBS) after gross total resection of brain metastases [45], which indicate a superior outcome in the treatment arm. *CI* confidence interval

tion how far the CTV should extend beyond the edges of the resection cavity to account for any residual nests of infiltrating neoplastic cells in the brain adjacent to the original tumor margin. It is an important issue, since invasion beyond the glial pseudocapsule was identified in 51–64% of BM, and its distance from the main tumor mass ranged between 12.5 and 450 μm in the autopsy studies and was up to 2 mm in the clinical series, with a variable propensity for infiltration depending on the cancer histology [46–48]. With these data in mind, operators contouring the CTV for BM should consider circumferential inclusion of a minimum of 2 mm of adjacent brain tissue, certainly if safety considerations permit. In the case of adjuvant SRS to a resection cavity with irregular margins, this may necessitate either a very complex treatment plan or one that achieves simplicity at the expense of including more adjacent brain tissue in the target volume.

Timing

The optimal timing for adjuvant SRS after resection of BM has not yet been determined, and the published data are somewhat contradictory. Shah et al. [49] have reported that the volume of the resection cavity tends to decrease gradually after surgery. In their series, patients who underwent SRS within 1 month after their initial postoperative MRI had a mean resection cavity volume reduction of 13%, in comparison with 61% in those who underwent SRS later ($P = 0.0003$). There was no difference in local recurrence between the two groups; thus, the authors suggested that waiting to perform adjuvant SRS may be beneficial as it allows delivery of irradiation to a smaller volume of the marginal brain tissue [49]. However, the opposite conclusions were drawn by Atalar et al. [50], who reported that the greatest resection cavity volume reduction (median 29%) occurred during the first 3 days after surgery. In their cohort, no additional statistically significant change in this parameter was noted over the next 30 days. Thus, they concluded that the absence of delayed cavity reduction eliminates any benefit of waiting longer than 1–2 weeks to perform adjuvant SRS after resection of BM [50]. Moreover, Patel et al. [51] observed a postoperative increase in the resection cavity volume (median 28%) during the time interval between surgery and SRS (median 20 days), with the largest cavities showing the smallest changes.

This mélange of results might be explained by inherent features (such as cancer histology), variability of resection cavity volumes, differences in the incidence of early recurrence (which varies from series to series), and, thus, differences in surgical technique, since early recurrence is less likely with en bloc tumor resection [21]. In a prospective trial by Mahajan et al. [45], in which all patients received adjuvant SRS within 30 days of surgery, no case of tumor recurrence within that time interval was noted. Therefore, it seems safe to conclude that adjuvant SRS should be done at some point between 3 and 30 days after resection of BM, with consideration given to waiting until local tissue swelling and tenderness caused by surgical manipulations have died down.

Neoadjuvant Radiosurgery

Since recently, administration of SRS for BM immediately prior to tumor resection has also been used at a number of centers. Because the genesis of such a treatment strategy came later than adjuvant SRS, fewer articles have been generated to show its promise (Fig. 4), with a significant contribution being made by the Southeast Radiation Oncology (SERO) Group.

Asher et al. [52] were the first to report results of neoadjuvant SRS before resection of BM and demonstrated local control rates of 86% and 72% at 12 and 24 months after treatment, respectively. In their series comprising 47 consecutive patients with 51 operated tumors, six of the eight failures were either in dural-based lesions or in neoplasms adherent to draining veins. Despite clear indications of worse local control with adjuvant SRS in cases of larger resection cavity volumes, differences in local control rates were decidedly present with neoadjuvant SRS but were less strongly emphasized in larger versus smaller neoplasms [52]. These initial findings were expanded by Patel et al. [53] in a multicenter, retrospective, comparative study, which included 180 patients with 189 resected BM treated with either neoadjuvant SRS (37%) or adjuvant SRS (63%). Multivariate analysis showed similar OS, local recurrence rates, and distant brain failure rates in the two cohorts, but leptomeningeal dissemination and symptomatic radiation necrosis were less frequent among patients who underwent neoadjuvant SRS [53].

In a subsequent multi-institutional analysis, Prabhu et al. [38] compared SRS alone with surgery combined with SRS for large BM (volume ≥4 cc or maximum diameter >2 cm). Their series included 213 patients with 223 treated tumors. SRS alone, neoadjuvant SRS followed by resection, and resection followed by adjuvant SRS were done in 30%, 28%, and 42% of cases, respectively. The local recurrence rate was significantly lower and OS was longer in patients who had combined treatment. Although there was no difference in local recurrence rates between neoadjuvant and adjuvant SRS (22.5% versus 19.1% at 1 year after treatment), the incidence of radiation necrosis was significantly higher in the latter group (22.6% versus 5% at 1 year after treatment) [38]. This may suggest (if confirmed) that more irregular geometry of a resection cavity, relative to that of an intact nonoperated BM, expands the volume of irradiated adjacent brain

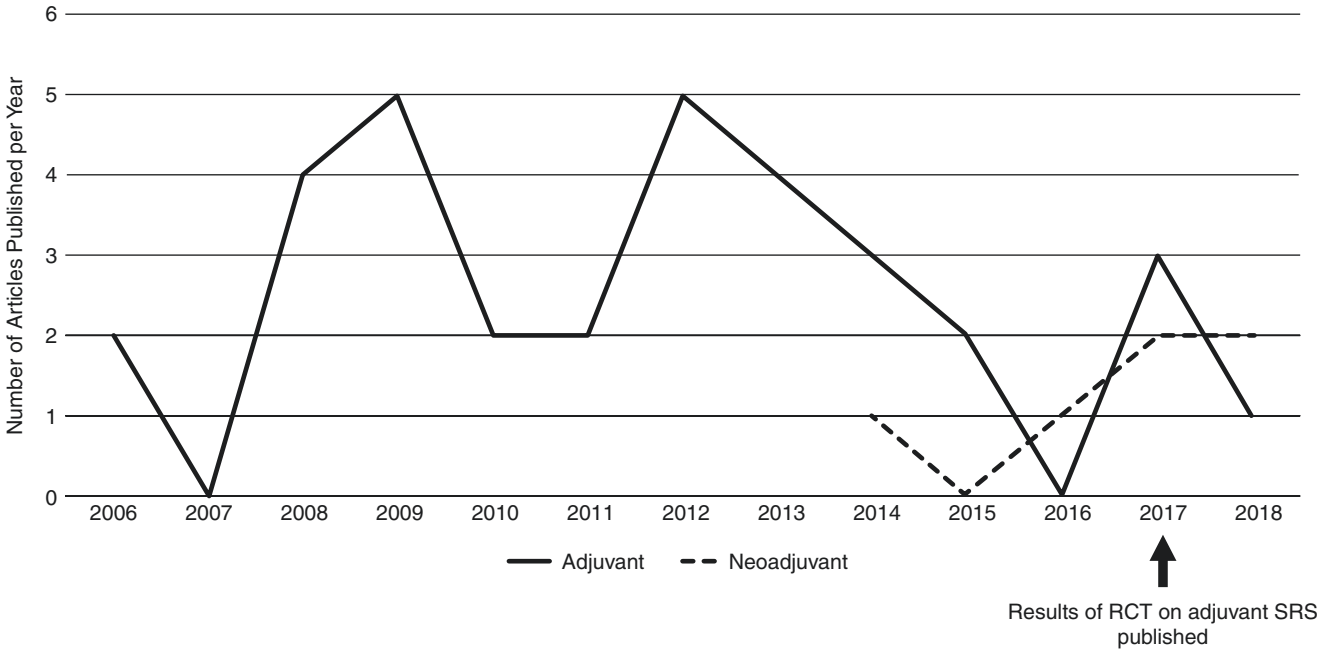


Fig. 4 Number of articles on adjuvant versus neoadjuvant stereotactic radiosurgery (SRS) in cases of surgery for brain metastases, published between 2006 and 2018. The graph illustrates the genesis of a therapy from the first rumbling of an idea and publication of results from small series, through generation of a prospective, randomized, controlled trial (RCT), which took 6 years (from 2011 to 2017) to complete [45]

tissue, and that this, in turn, increases the risk of radiation necrosis. This is a particularly important issue if the tumor sits in or adjacent to an eloquent brain region, where the impact of radiation injury can be especially severe; thus, techniques that are less likely to induce such complications are highly desirable.

In an additional study, Patel et al. [54] retrospectively compared the efficacy of neoadjuvant SRS with that of adjuvant WBRT in a series of 102 patients with 113 resected tumors. Treatment outcomes were similar in both groups, while the incidence of symptomatic radiation necrosis was slightly higher after neoadjuvant SRS (5.6% versus 0%) [54]. However, these results may have been influenced by the smaller lesion volumes and greater number of patients in the neoadjuvant SRS group. In addition, the patients' neurocognitive status after irradiation was not recorded; thus, it would be wise to avoid championing either of the treatment strategies used until supplementary data are available from future investigations.

Finally, one of the most recent reports by the same group highlights the outcome after neoadjuvant SRS before surgical removal of 125 BM in 117 patients [55]. At 2 years after treatment, 37% of patients were alive (median OS 17 months), and the overall incidence rates of local recurrence and symptomatic radiation necrosis were 25% and 4.8%, respectively. Subtotal tumor resection, which was done in only 4.8% of cases, was significantly associated with an increased risk of local failure, with a 6-month rate of 66.7% versus 6.5% after GTR ($P = 0.003$) [55]. These results are much more favorable than those from a small series of 12 patients treated at the University of Texas Southwestern Medical Center, none of whom survived at 2 years after treatment (the 12-month OS rate was 74%), and local recurrence was noted in 33% of cases at a mean of 5.4 months after surgery, with a tendency to develop in larger tumors [56].

Advantages and Disadvantages

One distinct advantage of neoadjuvant SRS is that its administration ensures patients gain the benefits of this treatment option, given that some individuals will be excluded from adjuvant SRS because of overly large resection cavities, systemic progression of cancer, or loss to follow-up. In addition, neoadjuvant SRS can be delivered more consistently in relation to surgery than can adjuvant SRS, which is more subject to the vagaries of postoperative recovery. Practical considerations also apply, since stereotactic frame placement may be more difficult or painful in a patient who has recently undergone craniotomy (that problem may eventually become moot, given the availability of frameless SRS).

According to its advocates, the theoretical benefits of neoadjuvant SRS include better delineation of the gross tumor volume (GTV) on imaging of an anatomically intact lesion, since its borders are more crisp and definable, and avoidance of the sometimes complex treatment planning required for coverage of an irregular resection cavity and its indistinct margins that typically follow surgical resection (Fig. 5). In addition, treatment volumes are smaller in the neoadjuvant

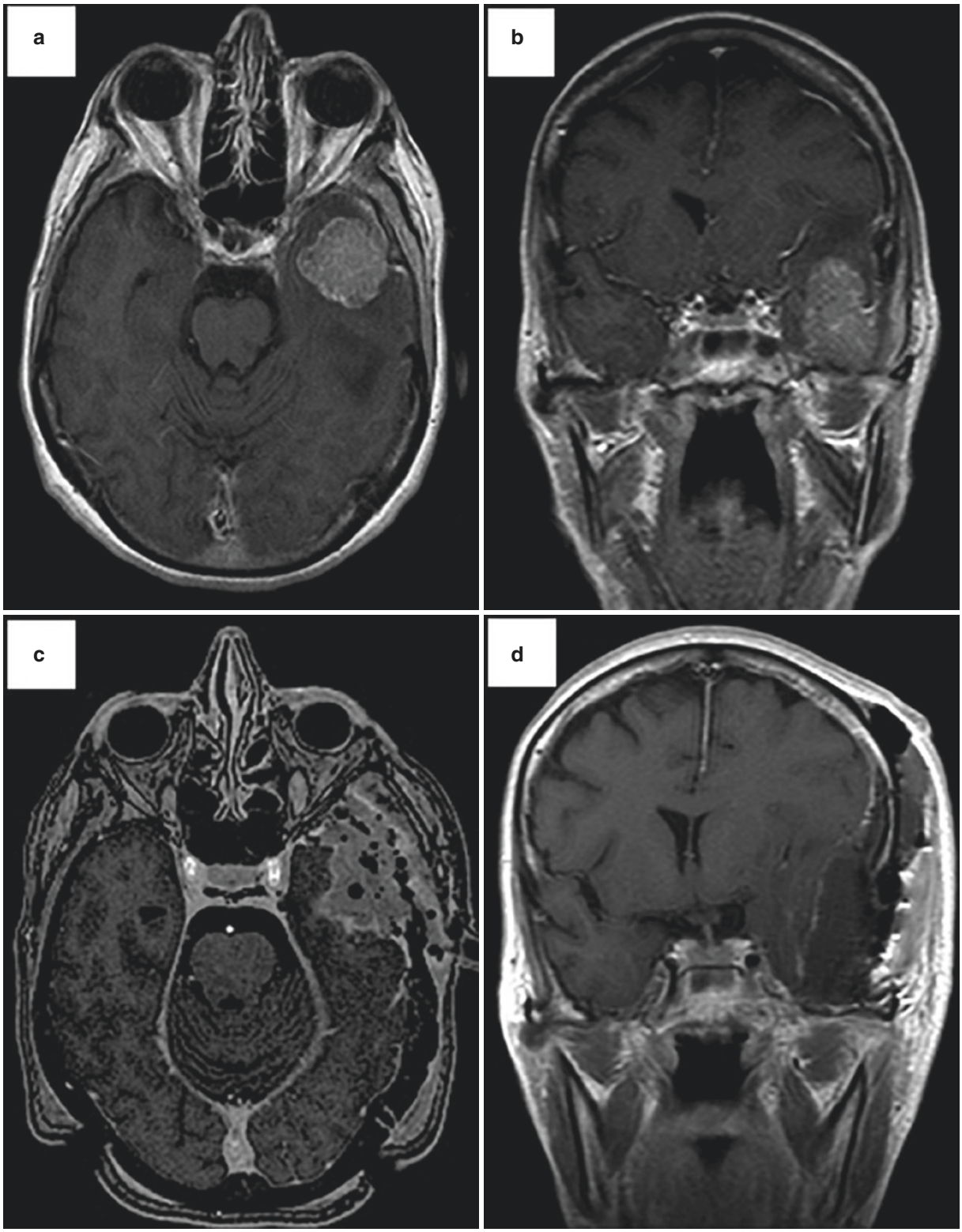


Fig. 5 A 61-year-old man afflicted with non–small cell lung cancer presented with a seizure and cognitive changes. Postcontrast T1-weighted magnetic resonance imaging (**a**, **b**) reveals a single dural-based intracranial metastasis occupying the left temporal lobe. The lesion is well delineated and relatively easy to contour for radiosurgery treatment planning, but it is large (maximum diameter >3 cm) and exerts a mass effect; thus, it needs to be removed for symptom control. After surgery, the resection cavity is much more complex and irregular in shape than was the original tumor (**c**, **d**), and although stereotactic radiosurgery (SRS) could still be done, treatment planning and radiation dosimetry will be more complicated and time consuming, and the target volume will probably include more adjacent normal brain tissue than would have been necessary had neoadjuvant SRS been applied. In the absence of clinical factors compelling upfront surgery, this is a good case for performing neoadjuvant SRS followed by tumor resection, rather than doing SRS in an adjuvant fashion

setting. When surgery is done after SRS, a portion of the irradiated brain tissue adjacent to the target is marginally resected, so less neuronal tissue remains in which radiation necrosis can be triggered. The theory has also been advanced that cancer cells within a possibly devascularized, edematous, hypoxic brain margin adjacent to a resection cavity will be less sensitive to the cytotoxic effects of adjuvant SRS [53]. Prevention of local recurrence and leptomeningeal dissemination is another important issue. The thing is that resection done in a piecemeal fashion may allow seeding of cancer cells into the nearby brain tissue or along the corridor of the surgical approach, and into the cerebrospinal fluid, which is more likely to occur in cases of surgery for cystic, hemorrhagic, or necrotic neoplasms. En bloc resection significantly less often induces such spillage; thus, it is the preferred method of BM removal. On the other hand, neoadjuvant SRS may pretreat cancer cells that are fated for seeding and it may prevent their survival either locally or in distant brain regions [53]. If this is true, neoadjuvant SRS would yield better suppression of targeted BM than adjuvant SRS. It is important to recognize, however, that each of these proposed "benefits" is purely speculative, as none of them has yet had its validity subjected to rigorous testing.

Possible negative features of neoadjuvant SRS include the absence of pathological confirmation of the diagnosis prior to initiation of treatment, and its potential for impairing healing of the irradiated tissues in the surgical wound. Finally, in cases of tumors with a prominent mass effect, surgical decompression is required for preservation of neurological function and to make other treatments safe; thus, BM that are very large or associated with significant perilesional brain edema will qualify for SRS only if surgery is done first.

Alternatives to Single-Session Radiosurgery

Although single-session, high-dose SRS is the treatment of choice for BM in both neoadjuvant and adjuvant settings, the merits of alternative methodologies should be considered as well. In cases of large neoplasms, multisession SRS or hypofractionated stereotactic radiotherapy (SRT) can provide higher cumulative doses (e.g., if given as 30 Gy in five fractions) than can single-session SRS (typically 15–18 Gy). According to published experience with adjuvant application of such a technique after surgery, treatment with typical use of three or five fractions results in 1-year local tumor control rates of 80–90%, accompanied by a variable incidence of radiation necrosis (from 0% to 9%) [57–67], which on the surface compares favorably with the results of the prospective, randomized, controlled trial of postoperative SRS versus observation after GTR of BM [45]. However, given the reported diversity of the doses, fractionation schedules, and interfraction timing, as well as the heterogeneity of patient populations in the series presented to date, a randomized study will be required in order to prove the superiority of multisession SRS.

Which Treatment Strategy Is Better?

With the exception of the two published randomized trials of adjuvant SRS [11, 45], all other reported clinical series have suffered from unevenly distributed and uncontrolled heterogeneity, which can create biases and make valid comparisons between two treatment strategies difficult. In particular, all results on use of neoadjuvant SRS reported to date have been driven from retrospective, noncontrolled studies with the potential for bias inherent in any comparisons made within or between those analyses. For determining the relative utility and safety of preoperative versus postoperative SRS and clarification of whether either of these two strategies confers better local tumor control and/or longer OS, a well-powered, head-to-head, prospective, randomized trial is mandatory. It would start with carefully and consistently defining when irradiation should be done in relation to the date of surgery, and with creating subgroups of resection types (en bloc versus piecemeal without a radiographic residual tumor versus piecemeal with a radiographic residual tumor) for analysis. Endpoints to examine in any future comparative studies must include the incidence rates and time to events, such as local recurrence, distant brain failure, symptomatic radiation necrosis, and leptomeningeal dissemination. Ideally, neurocognitive assessments, both before and after treatment, should also be included in the analysis. One such trial (clinicaltrials.gov identifier NCT03741673) is currently ongoing at the MD Anderson Cancer Center [68]. However, given that the prospective study by Mahajan et al. [45] took 6 years to complete, the question of which treatment strategy is better will not be settled soon. Moreover, it may ultimately be shown that the best tumor control rates and fewest complications arise with multisession SRS or hypofractionated SRT instead of single-session treatment.

Interplay of Immunomodulation and Radiosurgery

The advent of immunotherapy in oncology has some relevance to the optimal timing of SRS. Immunomodulatory strategies of dual checkpoint blockade are being used currently with some success to treat small, asymptomatic BM from melanoma and other cancers [69]. As many patients now come to SRS while on immune checkpoint inhibitors,

and because radiation necrosis may in some cases be provoked or worsened by local treatment-induced immune dysregulation, many centers are watching such cases closely to gain a better understanding of the interplay (or lack thereof) between immunomodulation and SRS. One cautionary case has been reported of a patient on nivolumab prior to neoadjuvant SRS, who began a further course of nivolumab and ipilimumab 14 days after the associated surgery [70]. One day later, he developed a severe inflammatory reaction around the resection cavity, and MRI showed a radiographic appearance that suggested a brain abscess. The enhancement and edema faded relatively promptly with steroid treatment. This reaction might have occurred regardless of the preceding SRS, but the possibility of potentiation of such neuroinflammation by irradiation cannot be entirely discounted [70]. On the other hand, it has been demonstrated that concomitant use of immune checkpoint inhibitors and SRS does not increase peritumoral edema or the incidence of radiation necrosis in patients with BM from NSCLC [71], and it may indeed improve local and regional tumor control in patients with metastatic melanoma [72]. To date, no evidence has been presented regarding any differences in clinical outcomes from such concurrent therapy relating to the use of SRS before versus after surgery.

As immunotherapy can be either locally immunosuppressive or immunogenic, and additionally can provoke an abscopal effect (which in animal models is dependent on the time interval between neoadjuvant radiotherapy and surgery), the effects of combined treatment remain a complex and unresolved issue [73, 74]. While it is unclear whether immune activation can be harnessed most effectively with neoadjuvant versus adjuvant SRS, the timing and dose of irradiation are likely to affect the balance of immune mechanisms within the neoplasm and its microenvironment, and even at distant sites. For instance, irradiation of mouse mesothelioma done 7 days before radical resection resulted in a much stronger incidence of tumor rejection than when it was done 1 day before surgery [74]. It seems likely that adjuvant SRS would be less immunogenic than that done prior to surgery, as the latter is delivered to the tumor at maximum volume and with its antigenic load intact, whereas postoperative irradiation targets mainly microscopic volumes of tumor mingled with normal brain tissue.

Conclusion

Because the only relevant, prospective, randomized, controlled trials done to date have established the superiority of adjuvant SRS to observation or WBRT after resection of BM, this treatment strategy has become the unofficial standard of care for patients with indications for surgery. At the same time, retrospective studies have indicated that neoadjuvant SRS may result in equivalent rates of local tumor control and comparable survival outcomes, with lower incidence of radiation necrosis and/or leptomeningeal dissemination, and may imply superiority to adjuvant SRS in terms of easier administration (in particular, due to avoidance of possible delays imposed by postoperative recovery) and reduction of patient discomfort during placement of a stereotactic frame on the intact cranium. Nevertheless, the relative merits of neoadjuvant SRS can be determined only by carefully controlled, prospective, randomized trials of its efficacy and safety. For now, adjuvant and neoadjuvant SRS show evidence of utility in achieving better local tumor control after surgical removal of BM in comparison with surgery alone, but no specific guidelines exist that favor one method over the other; thus, both should be considered beneficial in clinical care.

Conflict of Interest The author has no conflict of interest concerning the reported materials or methods.

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Redistributing Central Target Dose Hot Spots for Hypofractionated Radiosurgery of Large Brain Tumors: A Proof-of-Principle Study

Lijun Ma, Steve E. Braunstein, Encouse Golden, Shannon Fogh, Jean Nakamura, Michael W. McDermott, and Penny K. Sneed

Abstract *Objective:* The present proof-of-principle study investigated radiobiological effects of redistributing central target dose hot spots across different treatment fractions during hypofractionated stereotactic radiosurgery (HSRS) of large intracranial tumors.

Methods: Redistribution of central target dose hot spots during HSRS was simulated, and its effects were evaluated in eight cases of brain metastases. To assess dose variations in the target across *N* number of treatment fractions, a generalized biologically effective dose (gBED) was formulated. The gBED enhancement ratio was defined as the ratio of gBED in the tested treatment plan (with central target dose hot spot redistributions across fractions) to gBED in the conventional treatment plan (without central target dose hot spot redistributions).

Results: At a median α value of 0.3/Gy, the tested treatment plans resulted in average gBED increases of 15.6 ± 3.5% and 8.3 ± 1.8% for α/β ratios of 2 and 10 Gy, respectively. In comparison with conventional treatment plans, the differences in the Paddick conformity index and gradient index did not exceed 2%.

Conclusion: Redistributing central target dose hot spots across different treatment fractions during HSRS may be considered promising for enhancing gBED in the target. It may be beneficial for management of large intracranial neoplasms; thus, it warrants further clinical testing.

Keywords Biologically effective dose · Biological modeling · Hypofractionated stereotactic radiosurgery · Intracranial metastases · Targeting · Treatment planning

L. Ma (✉) · S. E. Braunstein · E. Golden · S. Fogh · J. Nakamura
P. K. Sneed
Department of Radiation Oncology, University of California San Francisco (UCSF), San Francisco, CA, USA
e-mail: lijun.ma@ucsf.edu

M. W. McDermott
Department of Neurosurgery, University of California San Francisco (UCSF), San Francisco, CA, USA

Introduction

Hypofractionated stereotactic radiosurgery (HSRS) has been implemented for minimally invasive management of large brain tumors, with promising local control rates and low treatment-related toxicity [1–13]. After introduction of the Leksell Gamma Knife Icon™ (Elekta AB; Stockholm, Sweden), HSRS may be applied for Gamma Knife surgery as well, and updated versions of Leksell GammaPlan® (Elekta AB) allow treatment planning and dosimetry of hypofractionated dose distributions with image-guided superposition of a large number of isocenters (>10) [14–18]. One of the distinctive features of such treatment is prominent dose inhomogeneity within the target, where hot spots may reach 200% of the prescription dose. As was demonstrated recently, inhomogeneous dose distribution may be associated with better local control of brain metastases (BM) after HSRS [19].

On the basis of our previous experience with optimization and redistribution of dose hot spots within a large target during single-session stereotactic radiosurgery (SRS) [20], in the present proof-of-principle study, we investigated whether the same strategy may be applied for HSRS.

Materials and Methods

Redistribution of central target dose hot spots during HSRS by means of the Leksell Gamma Knife Icon™ was simulated and evaluated in eight cases of large BM (volume >7 cc). For this purpose, the following strategy for treatment planning was employed. First, a treatment plan within a dose matrix covering the partial target volume (similar to planning for a volume-staged SRS) was created and optimized [21]. Second, the central target dose hot spots were adjusted by placing 4 mm isocenters inside the dose matrix according to a previously reported method [20]. Third, optimization of the treatment plan for the entire target volume

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*,
Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_10,

was continued by expansion of the dose matrix and gradual placement of isocenters outside the partially targeted volume, with subsequent iterative adjustment of their weights and locations with respect to dose distributions. Finally, the same process was repeated for another treatment fraction by shifting the dose matrix to another partial target volume.

Generalized Biologically Effective Dose Formula

To evaluate voxel-by-voxel spatial and temporal dose variations in the target across N number of different treatment fractions, a generalized biologically effective dose (gBED) was formulated.

First, the total survival probability (S) of the target volume was assumed as:

$$S = \sum_i v_i S\left(D_i\right) \tag{1}$$

where v_i is the ith fractional volume receiving a uniform fractional dose (D_i) (i.e., (v_i, D_i) forms the ith bin of the differential dose–volume histogram for the volume of interest (VOI)). If the ith fractional volume alone will be focused, the formula will be as follows:

$$S\left(D_i\right) = \prod_k e^{-\alpha D_{k,i} - \beta D_{k,i}^2} = e^{\sum_k -\alpha D_{k,i} - \beta D_{k,i}^2} = e^{-\left(\alpha (D_i) + \beta (D_i)^2 + \beta N \delta_i^2\right)} \tag{2}$$

where $D_{k,i}$ is the dose to the ith volume for the kth fraction ($k = 1, 2, \ldots N$); D_i and δ_i are, respectively, the mean dose and standard deviation for the ith voxel averaged over N treatment fractions; and α and β are parameters from the standard linear–quadratic (LQ) model. Of note, if D_i values are identical across all treatment fractions, then $\delta_i = 0$; thus, Eq. (2) is rendered into the conventional LQ formula.

If we assume that $S = e^{-\alpha \mathrm{gBED}}$ considering that the biological effect characterized by Eq. (1) is reproduced regardless of spatial and temporal dose variations across different treatment fractions, then gBED can be solved analytically as:

$$\mathrm{gBED} = -1/\alpha \times \log\left(\sum v_i S_i\right) \tag{3}$$

Comparative Analysis

For comparative analysis, the gBED enhancement ratio was defined as the ratio of gBED in the tested treatment plan (with central target dose hot spot redistributions across fractions) to gBED in the conventional treatment plan (without central target dose hot spot redistributions). Of note, corresponding to the purpose of the study, the conventional treatment plan was specifically defined as any fractionated treatment plan that would yield a maximum gBED value if applied consistently during the entire treatment course. Since gBED depends on α and β values, the ranges of the α value from 0.1/Gy to 0.5/Gy (median 0.3/Gy) and of the α/β ratio from 2 to 20 Gy were considered to account for both slow- and fast-growing tumors. Differences in the Paddick conformity index [22] and gradient index [23] in the radiosurgical plans created according to two compared treatment strategies were also analyzed.

Results

The tested treatment plans (with central target dose hot spot redistributions across fractions) consistently produced higher gBED values in the target volume. As an example, Fig. 1 shows the dependence of the gBED enhancement ratio on various α values and α/β ratios in one of the studied cases. Increases in both the α values and α/β ratios resulted in a decrease in the gBED enhancement ratio. At a median α value of 0.3/Gy, the tested treatment plans resulted in average gBED increases of 15.6 ± 3.5% and 8.3 ± 1.8% for α/β ratios of 2 and 10 Gy, respectively (Fig. 2).

Redistributions of dose hot spots across treatment fractions did not affect the target coverage; additionally the differences in the Paddick conformity index and gradient index did not exceed 2% (Fig. 3; Table 1).

Discussion

During conventional HSRS, central target dose hot spots are generally kept in the same position during the entire course of treatment. However, they may be redistributed within the target volume across different treatment fractions (thus allowing for spatial and temporal dose variations during sequential treatment sessions). Our proof-of-principle study was directed at evaluation of the radiobiological effects of such a novel strategy for HSRS.

The results presented herein have demonstrated that in comparison with a conventional treatment plan (without central target dose hot spot redistributions), the tested treatment plan (with central target dose hot spot redistributions across fractions) significantly increases gBED. It may potentially have a positive impact on the effectiveness of HSRS, particularly in cases of large intracranial tumors for which

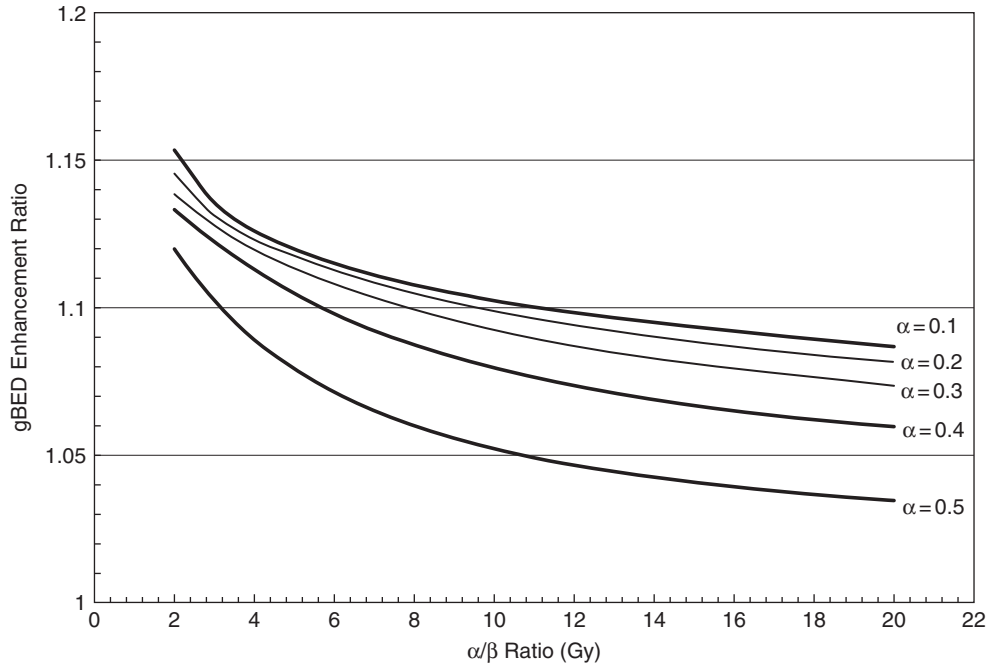

Fig. 1 Dependence of the generalized biologically effective dose (gBED) enhancement ratio on various α values (ranging from 0.1/Gy to 0.5/Gy) and α/β ratios (ranging from 2 to 20 Gy) in one of the studied cases. Note: increases in both the α value and the α/β ratio result in a decrease in the gBED enhancement ratio

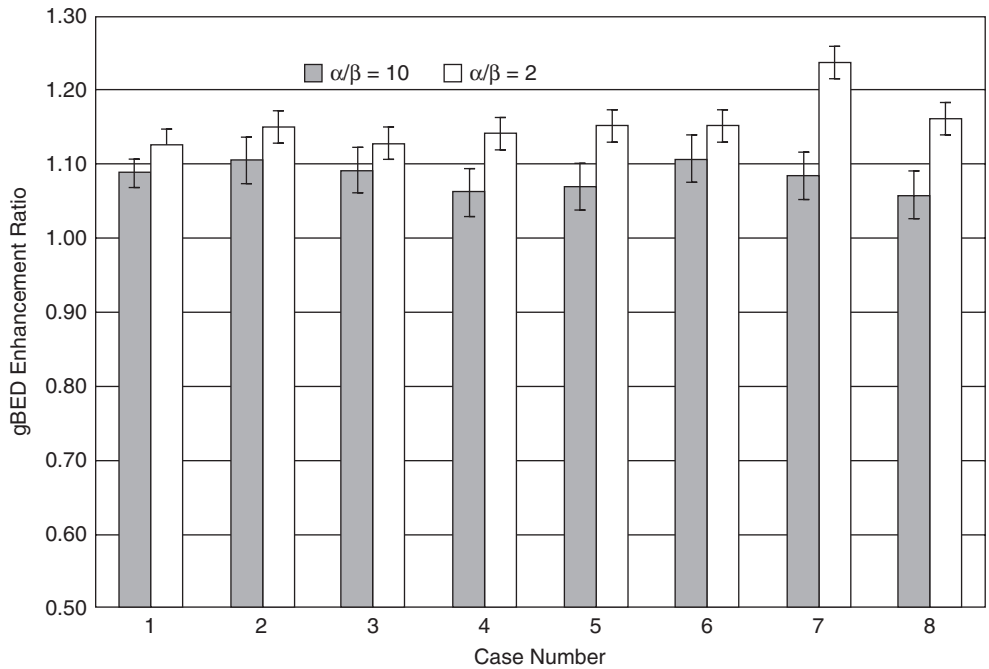

Fig. 2 Generalized biologically effective dose (gBED) enhancement ratio in all studied cases at an α value of 0.3/Gy. Note: the gBED enhancement ratio consistently exceeds 1.00 (reflecting the radiobiological advantages of the tested treatment plans with central target dose hot spot redistributions across different treatment fractions) and it is higher for lower α/β ratios (e.g., 2 versus 10 Gy, as shown herein)

application of high prescription doses is hardly reliable, since it translates into an increase in the adjacent normal brain radiation dose due to the power law governing peripheral isodose volumes [24]. In fact, the revealed rise in gBED associated with redistribution of central target dose hot spots corresponds to an increase of approximately 10% in the prescription dose if a conventional treatment plan is used (i.e., equivalent to delivery of an extra 2–3 Gy radiation dose during standard HSRS of 25 Gy in five fractions, but without any increase in the adjacent normal brain radiation dose). Moreover, the increase in gBED was most prominent at low α/β ratios, which suggests that the radiobiological advantages of the tested treatment strategy may be most prominent in cases of slow-growing tumors (e.g., meningi-

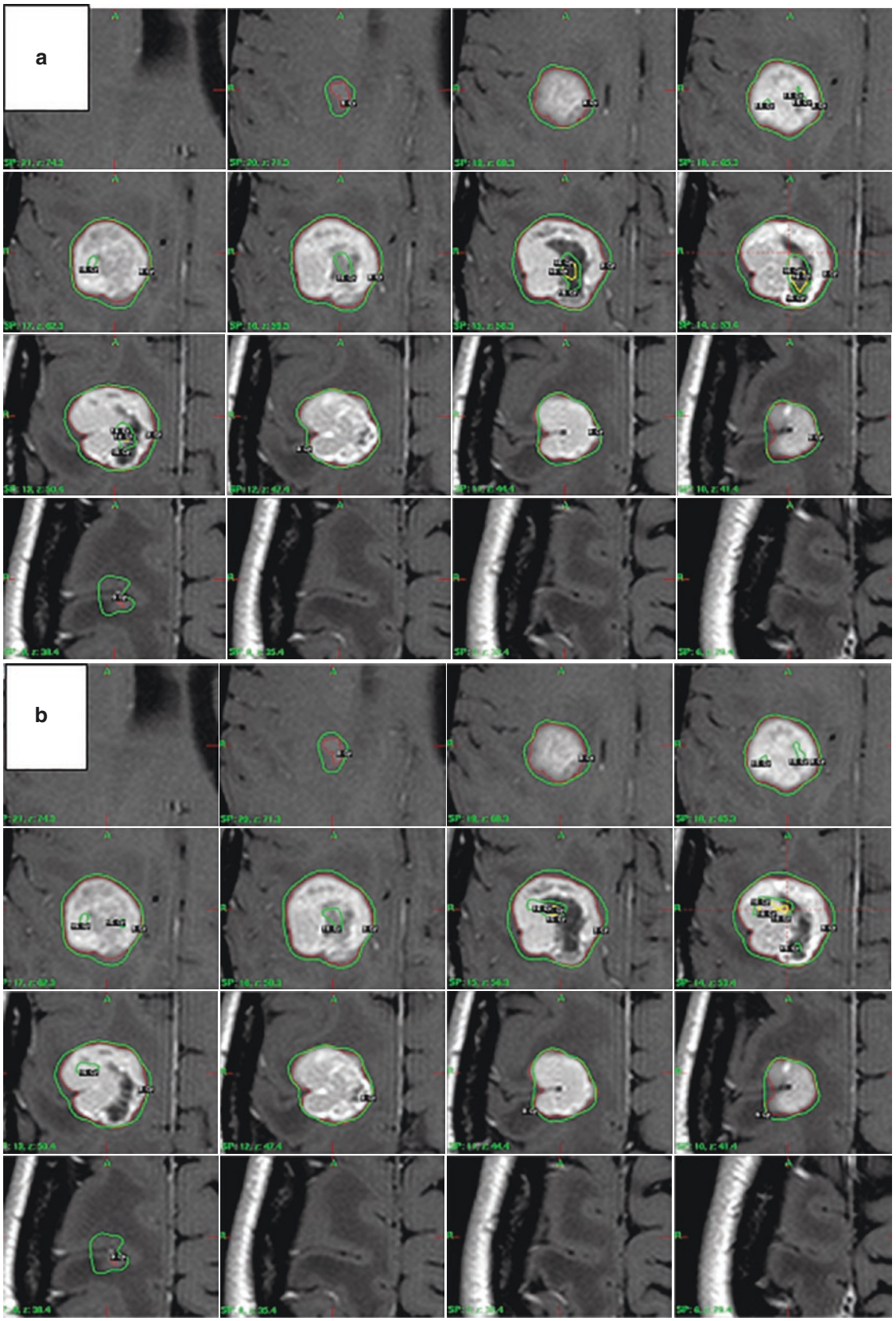

Fig. 3 Central target dose hot spot redistribution between two different treatment fractions (**a** and **b**) in a case of large brain metastasis. Note the absence of significant changes in the target coverage and conformity

Table 1 Comparative parameters of the evaluated treatment plans in all studied cases

		Coverage		Paddick conformity index		Gradient index		gBED enhancement ratio (at $\alpha = 0.3$/Gy)	
Case number	Target volume (cc)	TTP	CTP	TTP	CTP	TTP	CTP	α/β ratio = 10 Gy	α/β ratio = 2 Gy
1	15.1	0.99	0.99	0.82	0.82	2.74	2.76	1.09	1.13
2	22.1	0.99	0.99	0.73	0.73	2.81	2.83	1.10	1.15
3	21.1	0.98	0.98	0.73	0.71	2.70	2.69	1.09	1.13
4	16.2	0.98	0.98	0.81	0.80	2.88	2.89	1.06	1.14
5	11.3	0.98	0.98	0.66	0.65	2.92	2.93	1.07	1.15
6	15.6	0.99	0.99	0.82	0.83	2.67	2.69	1.11	1.15
7	7.7	0.97	0.97	0.82	0.82	2.91	2.93	1.08	1.24
8	8.6	0.99	0.99	0.87	0.86	2.86	2.85	1.06	1.16

CTP conventional treatment plan (without central target dose hot spot redistributions), *gBED* generalized biologically effective dose, *TTP* tested treatment plan (with central target dose hot spot redistributions across fractions)

oma) in comparison with fast-growing tumors (e.g., BM). Finally, redistributions of dose hot spots across fractions did not affect the quality of radiosurgical treatment plans with regard to the target coverage, Paddick conformity index, and gradient index, and these findings are consistent with the results of our previous studies [20, 24].

Conclusion

Redistribution of central target dose hot spots across different treatment fractions during HSRS for intracranial tumors may be considered promising for enhancing gBED in the target and does not have any negative impact on the qualitative parameters of the radiosurgical treatment plan. It may be beneficial for management of large neoplasms. Further clinical studies should demonstrate whether the observed radiobiological advantages of the suggested treatment strategy for intracranial HSRS are translatable into improved local tumor control and a better clinical outcome.

Conflict of Interest Dr. Ma has previously received an educational honorarium and travel support from Elekta AB. The other authors have no conflict of interest concerning the reported materials or methods.

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Possible Overcoming of Tumor Hypoxia with Adaptive Hypofractionated Radiosurgery of Large Brain Metastases: A Biological Modeling Study

Lijun Ma, Chia-Lin Tseng, and Arjun Sahgal

Abstract *Objective:* The present biological modeling study evaluated possible application of adaptive hypofractionated stereotactic radiosurgery (HSRS), which involves escalation of the prescription dose according to the gradual decrease in the tumor volume between treatment sessions separated by 2- to 3-week intervals, in the management of large brain metastases.

Methods: To investigate the effects of dose escalation during three-stage adaptive HSRS, a generalized biologically effective dose (gBED) model was applied. Accounting for both a nonuniform dose distribution inside the target and tumor hypoxia was implemented, and normal brain radiation dose distributions were assessed.

Results: In comparison with conventional three-stage HSRS (with an identical prescription dose of 10 Gy at each treatment session), adaptive HSRS resulted in a 30–40% increase in gBED. This effect was especially prominent in late-responding targets (with α/β ratios from 3 to 10 Gy) and in neoplasms containing a high percentage of hypoxic cells. Despite dose escalation in the target, irradiation of the adjacent normal brain tissue was kept within safe limits at a level similar to that applied in conventional three-stage HSRS.

Conclusion: Adaptive HSRS theoretically results in significant enhancement of gBED in the target and may possibly overcome resistance to irradiation, which is caused by tumor hypoxia. These advantages may translate into higher treatment efficacy in cases of large brain metastases.

L. Ma (✉)
Department of Radiation Oncology, University of California San Francisco (UCSF), San Francisco, CA, USA
e-mail: lijun.ma@ucsf.edu

C.-L. Tseng · A. Sahgal
Department of Radiation Oncology, Sunnybrook Odette Cancer Centre, Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada

Keywords Biologically effective dose · Biological modeling · Hypofractionated stereotactic radiosurgery · Intracranial metastases · Treatment planning · Tumor hypoxia

Introduction

Single-session stereotactic radiosurgery (SRS) is highly effective in management of small (<2 cm in diameter) brain metastases (BM), whose local control rates are approaching 70–80% [1–4]. However, in cases of large tumors (>2–3 cm in diameter), the effectiveness of such treatment is steadily decreasing [3, 5–9]. Ideally, higher radiation doses should be delivered to larger neoplasms to counteract the greater burden of pathological tissue for effective achievement of local growth control. However, an increase in the irradiated tumor volume results in a corresponding increase in the irradiated volume of adjacent normal brain tissue, whose tolerance is determined by the total prescription dose and dose per fraction. Thus, for avoidance of radiation-induced injury, the prescription dose delivered during single-session SRS should be limited. The Radiation Therapy Oncology Group (RTOG) 90-05 study showed that for maintenance of acceptable toxicity rates during such treatment, brain tumors with maximum diameters of ≤2, 2.1–3, and 3.1–4 cm should receive the maximum prescription doses of 24, 18, and 15 Gy, respectively [7]. A decrease in the prescription dose in turn results in worse local control. Moreover, large malignant neoplasms are typically characterized by prominent tissue hypoxia, which further limits the therapeutic effects of irradiation.

To increase the biologically effective dose (BED) delivered to large targets while respecting normal brain tissue tolerance, the concept of hypofractionated stereotactic radiosurgery (HSRS) has been developed. Usually, it is based on delivery of a total prescription dose of 24–30 Gy, separated into 3–5 equal, consecutive or closely scheduled

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*,
Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_11,

daily fractions [6]. An extreme variation of HSRS, also known as staged SRS, involves longer intervals between treatment sessions (e.g., 2–3 weeks). During such treatment, the tumor may demonstrate prominent shrinkage [5], which requires radiosurgical replanning before each stage of irradiation. Taking this fact into consideration, we have hypothesized that in such cases, the prescription dose may be escalated according to the observed decrease in the target volume while maintaining identical normal brain tissue dose distributions within safe limits (the concept of adaptive HSRS). The rationale for such a treatment strategy is based on attainment of a nonuniform dose distribution within the target, which could possibly overcome resistance to irradiation, caused by tumor hypoxia [10]. The present biological modeling study specifically investigated to what extent the prescription dose could be escalated, considering the variable distributions of the central target dose hot spots and the levels of hypoxia within the neoplasm, and whether dose escalation may theoretically provide any significant advantages over conventional HSRS for large BM.

Materials and Methods

To investigate the effects of dose escalation during adaptive HSRS of large BM and the theoretical impact of tumor hypoxia on the response to such treatment, a previously described model of generalized BED (gBED) [11] was applied. The concept and formulation of gBED for modeling of nonuniform dose distributions during SRS and stereotactic body radiation therapy (SBRT) have been reported by our group previously [11, 12]. One of the most important features is that the composite gBED for the entire treatment course during HSRS represents the sum of the gBED values of all treatment sessions, which is similar to the standard BED formula for irradiation with uniform doses during conventional fractionated radiotherapy [11].

The total survival probability (S) of a target volume receiving a nonuniform dose is expressed as:

$$s = \sum_i v_i S\left(D_i\right) \tag{1}$$

where v_i is the ith fractional volume receiving a uniform fractional dose (D_i) (i.e., (v_i, D_i) forms the ith bin of the differential dose–volume histogram for the volume of interest (VOI)). According to the standard linear–quadratic (LQ) model:

$$S_i = \exp\left(-\alpha BED_i\right) \tag{2}$$

where BED_i corresponds to the ith fractional volume. Therefore, gBED may be defined as the dose that would produce an identical total S value for the whole target volume as:

$$S = e^{-\alpha \cdot gBED} = \sum_i v_i S_i = \sum_i v_i e^{-\alpha \cdot BED_i} \tag{3}$$

Assuming that the α/β ratio for a given target is constant, Eq. (3) may be further solved as:

$$gBED = -1/\alpha \times \log\left(\sum_i v_i e^{-\alpha \cdot BED_i}\right) \tag{4}$$

where $BED_i = ND_i\,[1 + G_i D_i / (\alpha / \beta)]$; correspondingly, N is the total number of treatment sessions (fractions) and G_i is the dose rate correction factor, whose formulation has been described by our group before [13].

Dose Escalation in the Target and Control for Irradiation of Normal Brain Tissue

In the present study for determination of the appropriate prescription dose, a general dose falloff formula [14, 15] was used. The interrelationships between the normal brain volume (V) surrounding the target and the delivered marginal isodose (D) are generally described as:

$$V/V_t = CI \cdot \left(D/D_t\right)^{\gamma} \tag{5}$$

where V_t is the target volume, D_t is the prescription dose, CI is the conformity index, and γ is an empirical fitting parameter with an approximate value of -1.5, which is accepted for most radiosurgical modalities, including a linear accelerator (LINAC) and Leksell Gamma Knife Perfexion™ (Elekta AB; Stockholm, Sweden).

As follows from Eq. (5), for any relative decrease in the target volume (V_t) by Δ at the time of the 2nd, 3rd, … Nth treatment session (fraction), in order to maintain the identical dose–volume relationship of the original treatment plan, the corresponding relative increase in the prescription dose (D_t) would be computed as $(1 - \Delta)^{1/\gamma}$. For example, if a dose of 10 Gy was delivered at the first treatment session, and after a 2-week interval, the target volume decreased by 25% (i.e., it constituted 75% of the original volume), then the corresponding escalated prescription dose, still maintaining the

same peripheral isodose distribution as that applied at the time of initial treatment, would be:

$$10\times\left(1-0.25\right)^{-1/1.5}=12\,\text{Gy}.$$

Likewise, any further decrease in the target volume at the time of subsequent treatment sessions could also be accounted for in a similar fashion for adaptive dose escalation based on the actual target volume.

Accounting for Tumor Hypoxia

For evaluation of and accounting for tumor hypoxia, the hypoxia reduction factor (HRF) suggested by Carlson et al. [16] was utilized. If HRF_i for the ith fractional volume was applied, then, without losing the generality of all of the derivations, BED_i in Eq. (4) would be rendered as:

$$BED_i = ND_i \,/\, HRF_i\left[1+G_iD_i\,/\left(HRF_i\alpha\,/\,\beta\right)\right] \qquad (6)$$

Since the exact HRF_i distribution within the target during treatment was unknown, all corresponding voxels were randomly sampled with the assumption that the total hypoxic cell concentration does not exceed a fixed percentage of the total target volume (e.g., 30%, 50%, 70%, or 80%) and that any hypoxic voxel possesses a high HRF_i value of 2.0–2.8. Of note, HRF depends on oxygenation but reaches 2.8 for maximum anoxic conditions.

Comparative Analysis

For comparative analysis, the gBED enhancement ratio was defined as the ratio of gBED in the tested treatment plan for three-stage adaptive HSRS (with prescription dose escalation at each stage according to the reduction in the tumor volume) to gBED in the treatment plan of three-stage conventional HSRS (with an identical prescription dose of 10 Gy at all stages).

Results

A simulation of adaptive HSRS for a large BM of unknown origin is illustrated in Fig. 1. The actual treatment was done with three-stage HSRS (total prescription dose 30 Gy), and the treatment sessions were separated by 2- to 3-week intervals. The initial tumor volume was 20 cc and was reduced to 11 cc by the time of the third treatment session. On the basis of the dose escalation concept described above, the prescription doses for adaptive HSRS should be 10, 12, and 15 Gy for the first, second, and third treatment sessions, respectively. This would result in normal brain dose distributions identical to that at the initial treatment session (e.g., an 8 Gy isodose volume of 21.2 cc).

During adaptive HSRS, the dose distributions within the target (also known as central target dose hot spots) differed at each replanned treatment session. However, despite such variations in dose patterns, the gBED enhancement ratio showed similar characteristics (Fig. 2). It demonstrated minimal variability during modeling of adaptive HSRS in 200 independent samples with randomly distributed hypoxic voxels; the maximum standard deviation of the values was ≤4% and mainly depended on the correspondence of hypoxic voxels to dose hot spots within the target. At the same time, the gBED enhancement ratio showed dependence on the α/β ratio and the percentage of hypoxic cells within the target volume; it demonstrated the highest values if the α/β ratio was within 3–10 Gy (i.e., in late-responding targets) and in modeled cases with a higher percentage of hypoxic cells. For example, for a target with an α/β ratio of 5 Gy, application of adaptive HSRS escalated the total gBED value by 38.1 ± 1.2% in the case of fully oxygenated tissue (0% hypoxic voxels) and by 46.7 ± 3.5% in the case of highly hypoxic tissue (80% hypoxic voxels randomly distributed within the target).

Discussion

Different strategies have been developed for delivery of sufficiently high prescription doses to large BM for improvement of their local control after SRS. For example, Minniti et al. [6] applied HSRS (three daily fractions of 9 Gy each) in tumors with a median volume of 12.5 cc. Comparison of such treatment with single-session SRS for relatively smaller neoplasms (median volume 8.8 cc) revealed that HSRS was accompanied by a halved incidence of adverse radiation effects (ARE) (9% versus 18%, $P = 0.01$) and better local tumor control rates (91% versus 77%, $P = 0.01$) [6]. Higuchi et al. [5] successfully used three-stage SRS for management of BM with a volume >10 cc (mean volume 17.6 cc, which was much larger than that in the aforementioned series reported by Minniti et al. [6]). The total prescription dose was 30 Gy (10 Gy at each stage), and the treatment sessions were separated by 2-week intervals. The vast majority (>90%) of tumors in this series ($N = 43$) demonstrated prom-

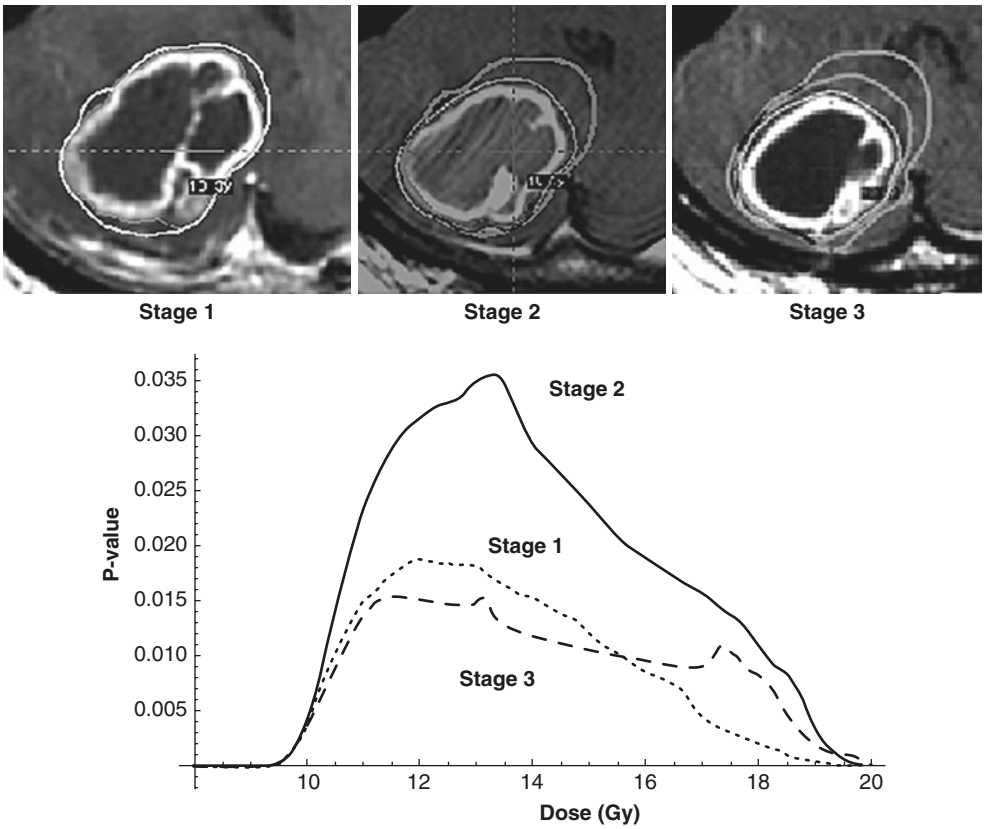

Fig. 1 Simulated three-stage treatment of a large brain metastasis of unknown origin, according to the concept of adaptive hypofractionated radiosurgery. Prescription isodose lines for each treatment session are shown on postcontrast T1-weighted magnetic resonance imaging (*top*), demonstrating a gradual reduction in the tumor volume. The differential dose–volume curves (*bottom*) suggest dissimilar variations in the probability density function of the dose distributions within the target volume for each replanned treatment session

inent shrinkage during treatment and, at the time of the second and third stages, their mean volume had decreased by 18.8% and 39.8%, respectively. ARE were noted in 9% of cases, and the 1-year local tumor control rate was 76%. [5].

Our group has developed a novel concept of adaptive HSRS for large intracranial neoplasms, which can be accomplished by means of any radiosurgical modality and involves creation of a new treatment plan at each stage of irradiation (separated by 2- to 3-week intervals), delivery of a ≥10 Gy prescription dose per treatment session, and dose escalation according to the gradual decrease in the tumor volume. This results in highly nonuniform dose distributions within the target, which, as was suggested by Ruggieri et al. [10], may be effective for overcoming resistance to irradiation caused by tissue hypoxia.

The present study was directed at theoretical evaluation of adaptive HSRS for large BM, accounting for both a nonuniform dose distribution inside the target and the effects of tumor hypoxia. The latter was controlled by modeling with different hypoxic cell concentrations within the target volume. The results indicated that adaptive HSRS may indeed be notably advantageous, providing a 30–40% increase in gBED in comparison with conventional HSRS (which delivers identical prescription doses at all stages), and this may potentially translate into better local tumor control. The effect was especially prominent in late-responding targets with α/β ratios from 3 to 10 Gy and in neoplasms containing a high percentage of hypoxic cells. At the same time, despite dose escalation in the target, irradiation of adjacent normal brain tissue during adaptive HSRS was kept identical at the different treatment sessions, similarly to conventional three-stage HSRS (10 Gy per treatment session), and this corresponded well to safe limits. Such promising findings, along with inherent neuronal tissue repair mechanisms during sufficiently long time intervals between treatment sessions, may suggest that adaptive HSRS does not carry an increased risk of ARE.

There is no doubt that despite such beneficial results obtained in this theoretical study, the exact characteristics of adaptive HSRS with regard to its efficacy and safety may be established only in clinical investigations, preferably performed in a prospective and controlled fashion. In addition, there are several issues that require further clarification (e.g., the most appropriate number of treatment stages and the optimal time intervals between them). Moreover, while solid data suggest that application of the standard LQ formula is sufficiently appropriate for analysis of large-dose treatment [17, 18], this is still debatable and may be considered as a drawback of the presented predictive model. Nevertheless, since not

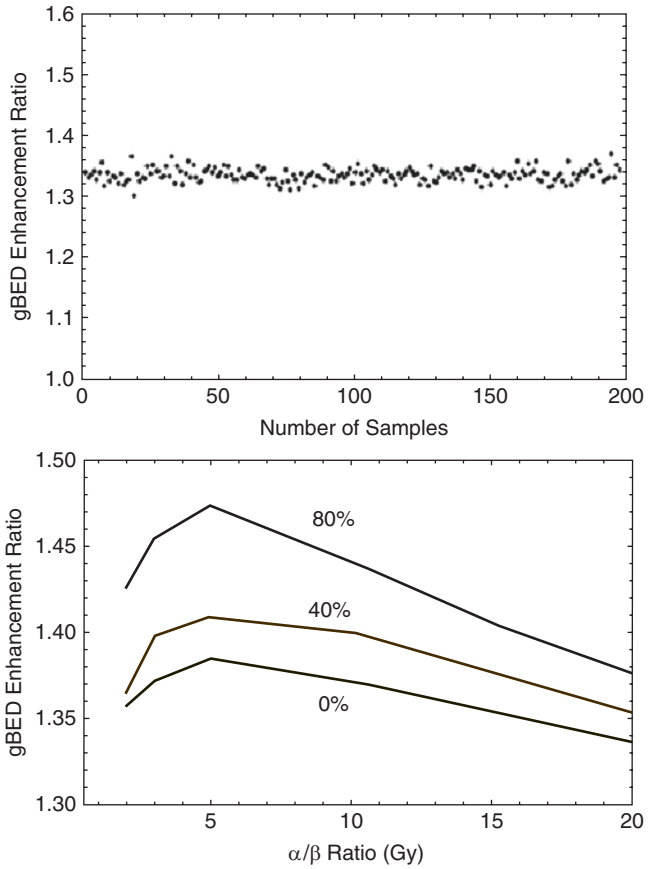

Fig. 2 Generalized biologically effective dose (gBED) enhancement ratio for adaptive hypofractionated radiosurgery in targets with a random distribution of hypoxic voxels. There is minimal variability in the values with regard to nonuniform dose distributions within the target volume during modeling in 200 independent samples (*top*) but a clear dependence (*bottom*) on the α/β ratio and the percentage of hypoxic cells (0%, 40%, and 80% as shown herein)

absolute gBED values but relative gBED enhancement ratios were computed from comparison of isodose distributions in treatment plans for adaptive and conventional HSRS, the reported results are sufficiently robust and the observed increase in total gBED (by approximately 30–40%) with the tested treatment strategy is accurate and compelling.

Conclusion

The suggested concept of adaptive HSRS based on escalation of the prescription dose according to the decrease in the tumor volume between treatment sessions theoretically results in significant enhancement of gBED in the target while maintaining delivery of a safe dose to adjacent normal brain tissue. Such a novel strategy may potentially overcome resistance to irradiation, which is caused by tumor hypoxia. These advantages may significantly increase treatment effectiveness during management of large BM; thus, further clinical evaluations of adaptive HSRS are warranted.

Conflict of Interest Drs. Ma and Sahgal have previously received educational honoraria and travel support from Elekta AB. Dr. Sahgal has received research grants from Elekta AB and has served on the medical advisory board of Varian Medical Systems.

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Differentiating Radiation-Induced Necrosis from Tumor Progression After Stereotactic Radiosurgery for Brain Metastases, Using Evaluation of Blood Flow with Arterial Spin Labeling (ASL): The Importance of Setting a Baseline

Elle A. Lambert and Stephen Holmes

Abstract *Objective:* This study evaluated the usefulness of arterial spin labeling (ASL) for assessment of tumor blood flow (TBF) and cerebral blood flow (CBF) before Gamma Knife surgery (GKS) for intracranial metastases, in order to analyze the variability of perfusion characteristics at baseline and to reveal how these data may impact differentiation of radiation-induced effects from tumor progression during follow-up.

Methods: Radiological data from 87 patients with intracranial metastases of solid cancers, who underwent TBF/CBF analysis by means of ASL at the Hawaii Advanced Imaging Institute between 2015 and 2018 both before and after GKS, were reviewed retrospectively. Only cases with a largest tumor diameter of ≥10 mm were included in the study cohort ($N = 53$).

Results: In comparison with CBF in the healthy contralateral cerebral cortex, TBF before GKS was greater in 32 cases (60%), lesser in 7 cases (13%), and equivalent in 14 cases (27%). There was significant variability in TBF both within and between histologically different groups of tumors.

Conclusion: Since, at baseline, approximately 40% of intracranial metastases have TBF that is lesser or equivalent to CBF, increased blood flow in the contrast-enhancing lesion after GKS may have insufficient sensitivity for identification of tumor progression. Availability of baseline TBF data may significantly facilitate differential diagnosis in such cases.

Keywords Arterial spin labeling · Baseline blood flow Follow-up imaging · Gamma Knife radiosurgery · Intracranial metastases · Macdonald criteria · Radiation-induced necrosis Stereotactic radiosurgery · Tumor progression

E. A. Lambert
St. George's, University of London at University of Nicosia, Nicosia, Cyprus

S. Holmes (✉)
InVision Imaging, Honolulu, HI, USA
e-mail: s.m.holmesmd@gmail.com

Introduction

Treatment of patients with intracranial neoplasms by means of chemotherapy, radiotherapy, stereotactic radiosurgery (SRS), or their combination may result in disruption of the blood–tumor barrier (BTB) and blood–brain barrier (BBB), leading to appearance or augmentation of lesion contrast enhancement and increases in enhancing lesion size, adjacent brain edema and the mass effect, which, however, do not correspond to true tumor progression [1–7]. There is general agreement that diagnosis in such complex clinical cases should be based on a multimodal approach with use of several metabolic and functional neuroimaging modalities, preferably applied in a longitudinal fashion [1]. Among the variety of modern imaging tools that can be utilized for this purpose, perfusion-weighted imaging (PWI) is one of the most effective [8].

Arterial spin labeling (ASL) is a PWI technique that allows both qualitative and quantitative evaluation of tumor blood flow (TBF) and cerebral blood flow (CBF). The usefulness of ASL for differentiating radiation-induced effects from brain tumor progression has been validated by several groups [3, 9–13]. Nevertheless, in previous investigations, perfusion measurements were rarely done at baseline before treatment. The objective of the present retrospective study was evaluation of TBF in brain metastases (BM) of solid cancers before Gamma Knife surgery (GKS) and analysis of how these data might impact imaging diagnosis during follow-up.

Materials and Methods

Radiological data from 87 patients with single or multiple BM, who underwent PWI by means of ASL at the Hawaii Advanced Imaging Institute (Honolulu, HI, USA) between

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*,
Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_12,

2015 and 2018 both before and after GKS, were reviewed retrospectively. The patients' primary cancers were located in the lung (in 40 cases), breast (in 15 cases), kidney (in 10 cases), skin (melanoma; in 7 cases), rectum (in 4 cases), bone (Ewing sarcoma; in 2 cases), and other organs (in 9 cases).

Pseudocontinuous ASL with dual postlabeling delay (PLD) times of 1.5 and 2.5 s was applied, frequently in combination with first-pass dynamic susceptibility-weighted contrast-enhanced (DSC) magnetic resonance imaging (MRI). Both qualitative color-coded maps and quantitative parameters of TBF and CBF were evaluated after coregistration of PWI with postcontrast T1-weighted MRI. The region of interest (ROI) was located in the area with the highest blood flow in the lesion and in the healthy contralateral cortex, and absolute TBF and CBF values (measured in milliliters per 100 g per minute) were obtained; the relative TBF (rTBF), defined as the TBF/CBF ratio, was also calculated. For avoidance of possible diagnostic errors caused by poor spatial resolution of the ASL technique in small neoplasms, only cases with at least one BM with a largest diameter of ≥10 mm were included in the study cohort ($N = 53$) for final analysis.

Results

There was significant variability in TBF both within and between histologically different groups of tumors (Fig. 1). BM of renal cell carcinoma (RCC) had relatively greater TBF than neoplasms of other origins. Overall, ASL-based measurement of TBF before GKS revealed that it was greater than (rTBF > 1), lesser than (rTBF < 1), and equivalent to (rTBF ≈ 1) CBF in the healthy contralateral cerebral cortex in 32 cases (60%), 7 cases (13%), and 14 cases (27%), respectively (Fig. 2). There was 92% agreement in perfusion measurements between ASL and DSC MRI.

Discussion

There is a widespread agreement that accurate discrimination of radiation-induced effects from progression of brain tumors after therapeutic irradiation remains one of the major unresolved diagnostic challenges of neuroradiology [4–6, 8, 10, 14–18]. Moreover, wide introduction of novel treatment modalities, including antiangiogenic therapy, molecular targeted therapy, and various types of immu-

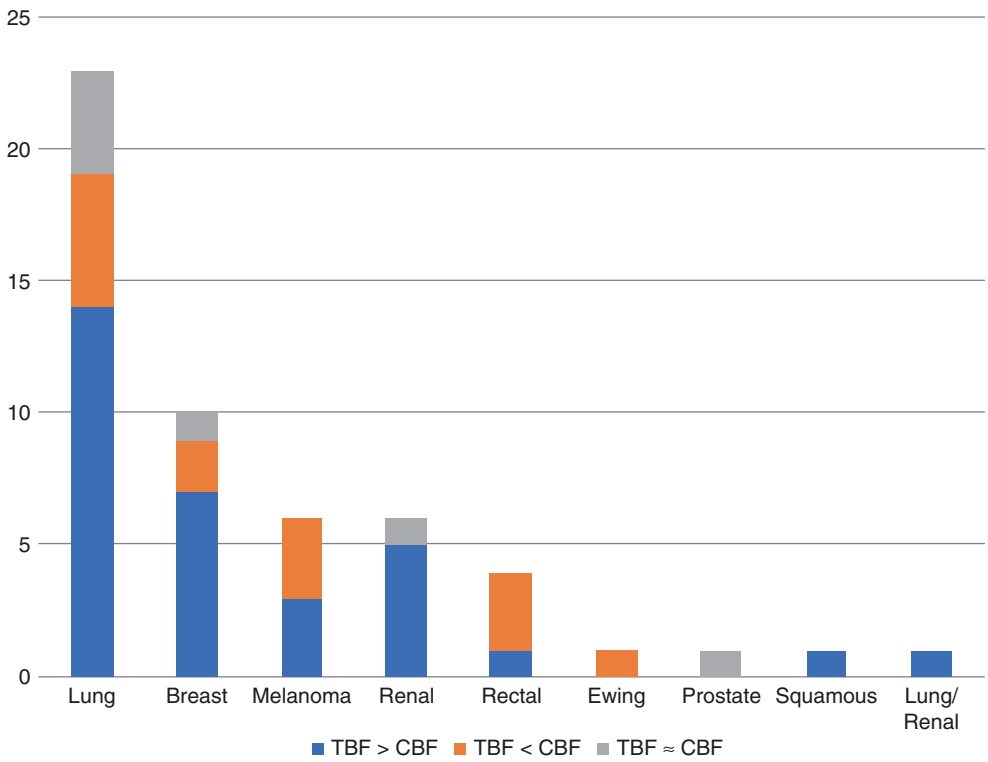

Fig. 1 Tumor blood flow (TBF) in intracranial metastases before Gamma Knife radiosurgery with regard to the location of the primary cancer. In comparison with cerebral blood flow (CBF) in the healthy contralateral cerebral cortex, TBF was greater, lesser, and equivalent in 60%, 13%, and 27% of cases, respectively

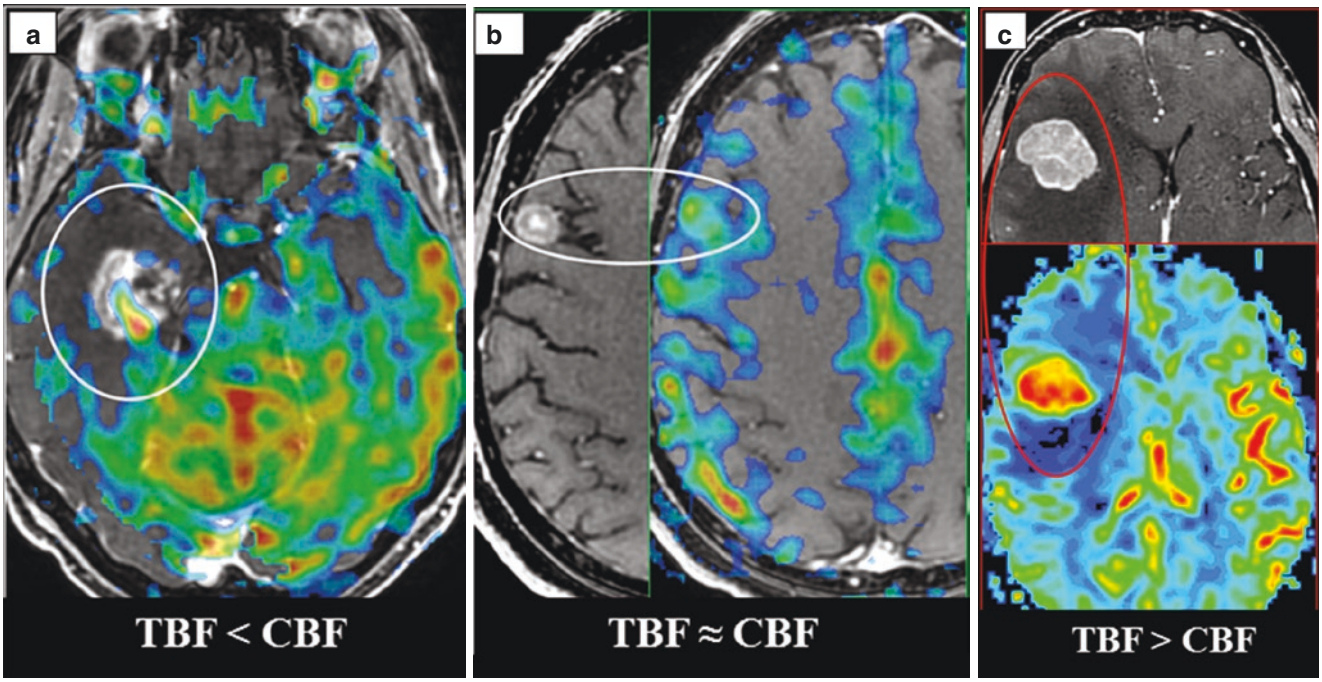

Fig. 2 Variability of perfusion characteristics in intracranial metastases before Gamma Knife radiosurgery. In comparison with cerebral blood flow (CBF) in the healthy contralateral cerebral cortex, these examples demonstrate lesser (**a**), equivalent (**b**), and greater (**c**) tumor blood flow (TBF)

notherapy—as well as their concomitant or adjuvant use along with radiotherapy or SRS—may make differentiation of the aforementioned pathological conditions much more complex or sometimes even impossible [5–8, 19]. As Belliveau et al. [14] stated, "introduction of new therapeutics has introduced new patterns of response that can confound interpretation of conventional MRI and can cause uncertainty in the proper management following therapy". Nevertheless, precise diagnosis in such cases is very important, since it not only determines the treatment strategy and subsequent follow-up but also has a direct impact on patient survival and quality of life [6, 10, 16, 19]. While radiation-induced necrosis may be controlled effectively with steroids, anticoagulants, hyperbaric oxygen therapy, or the antiangiogenic agent bevacizumab, tumor progression generally requires active anticancer chemotherapy, reirradiation, surgical resection, or combinations of these treatment modalities [2, 6, 10, 16, 19].

Differentiating Radiation-Induced Effects from Tumor Progression

For decades, imaging diagnosis during follow-up of patients with brain tumors after treatment was based on the Macdonald criteria [5, 16, 20, 21]. This method uses linear measurements of two cross-sectional diameters of the contrast-enhancing lesion and, on the basis of changes in their product in comparison with baseline, defines a complete response, a partial response, stable disease, or progressive disease. Appearance of new brain lesions, steroid doses, and the clinical status of the patient are also taken into consideration. Following its introduction in 1990 for evaluation of high-grade gliomas after adjuvant therapy [20], this diagnostic guideline quickly gained widespread acceptance by the neuro-oncology community and soon became the gold standard for diagnosis of brain tumor progression, being applied much more broadly than was intended initially.

Nevertheless, the inherent limitations of the Macdonald criteria and development of novel treatment modalities for which this method was hardly applicable (in particular, recognition of phenomena such as pseudoprogression and pseudoresponse) have resulted in an extensive search for new, more reliable methods for assessment of brain tumors after therapy [5–7, 10, 21, 22]. During the last decade, the Response Assessment in Neuro-Oncology (RANO) Working Group has developed updated criteria for evaluation of the treatment response in various intracranial neoplasms, including BM. However, even with application of these modern diagnostic guidelines, discrimination between tumor progression, pseudoprogression, and pseudoresponse remains challenging, and diagnostic problems in such cases have not been resolved completely (Fig. 3) [5, 21]. For example, in 2011, Patel et al. [16] reviewed MRI of 120 patients with BM who were followed up for 3 years after SRS with or without chemotherapy, and they found that the overall survival of patients with enlarged lesions was nearly twice that

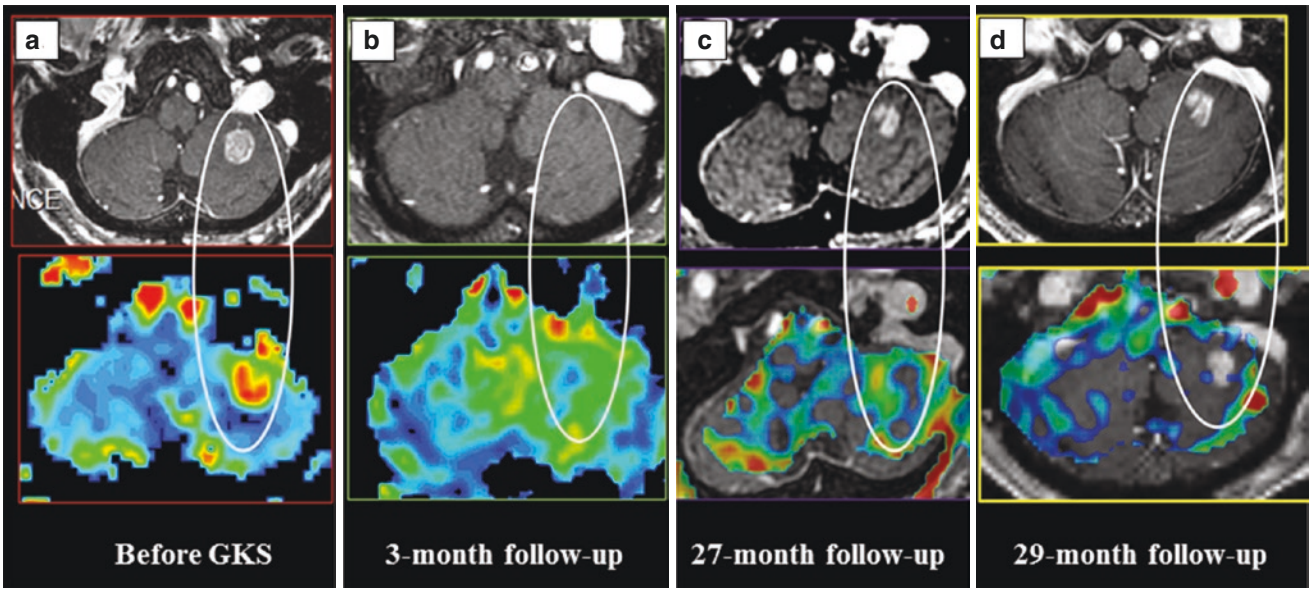

Fig. 3 Failure of structural postcontrast T1-weighted magnetic resonance imaging and value of perfusion-weighted imaging (PWI) by means of arterial spin labeling (ASL) in differentiating radiation-induced effects from tumor recurrence. An 86-year-old man underwent Gamma Knife surgery (GKS) for a metastasis in the left cerebellar hemisphere (marginal dose 22 Gy). Before treatment (**a**), the contrast-enhanced neoplasm clearly demonstrated increased perfusion. At 3 months after GKS (**b**), a complete response was noted with resolution of the abnormal area on PWI. At 27 months after GKS (**c**), the contrast-enhanced lesion reappeared within the irradiated field, but this was not accompanied by a local increase in blood flow. A radiation-induced effect was suspected and confirmed 2 months later when stable enhancement and perfusion patterns were demonstrated (**d**), Additional follow up imaging out to 4 years later was confirmatory

of patients with a stable or decreased mass volume (median survival 18.4 versus 9.5 months).

Challenges in differentiating radiation-induced effects from brain tumor progression necessitate use of novel methods, such as postcontrast MRI with evaluation of the T1/T2 match/mismatch and delayed-contrast extravasation MRI, as well as advanced metabolic and functional imaging modalities, including diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), proton magnetic resonance spectroscopy (MRS), various techniques of PWI and perfusion computed tomography (CT), and single-photon emission computed tomography (SPECT) and positron emission tomography (PET) with different radioisotope tracers. Their sensitivity and specificity vary within the range of 70–90%, but no single method provides 100% diagnostic accuracy [1, 3, 6, 8, 10, 12, 13, 17–19, 23–26]. Each of these techniques has advantages and shortcomings, and none of them is currently considered a gold standard. Even with a multimodal diagnostic approach (which is applied routinely in our own practice), establishment of the correct diagnosis may be difficult (Fig. 4). Of note, treatment-induced tissue changes may coexist closely with a viable neoplasm, which makes imaging diagnosis even more challenging [1, 5, 6, 8, 16, 19].

Meanwhile, studies on use of neuroimaging for differential diagnosis of treatment-induced effects and tumor progression have usually been based on relatively small numbers of cases, which has limited the power of their statistical analysis and general acceptance of their reported results. It is evident that for widespread clinical application, the efficacy of any novel imaging modality—in particular, allowing for acquisition of quantitative data—should be tested in a broad array of patients, using a standardized protocol in a multicenter setting [14].

Advantages of Perfusion Imaging with Arterial Spin Labeling

PWI has been validated by several groups as a sensitive and specific imaging modality, which can be used effectively for evaluation of patients with BM during follow-up after SRS. In particular, ASL is an easily applied and highly reliable technique, which corresponds well to the defined requirements of "next-generation imaging" [11, 14, 15, 27–29]. This modality may contribute significantly to the armamentarium of diagnostic methods because of its speed, safety, reproducibility, and ready availability, and it may be recommended as a standard part of every MRI investigation in patients with brain tumors—for example, during routine radiological follow-up after therapeutic irradiation. Such a strategy may provide important complementary diagnostic data and significantly increase the diagnostic yield, thus potentially resulting in health care savings due to timely establishment of the correct diagnosis, avoidance of additional work-up costs, and optimization of treatment.

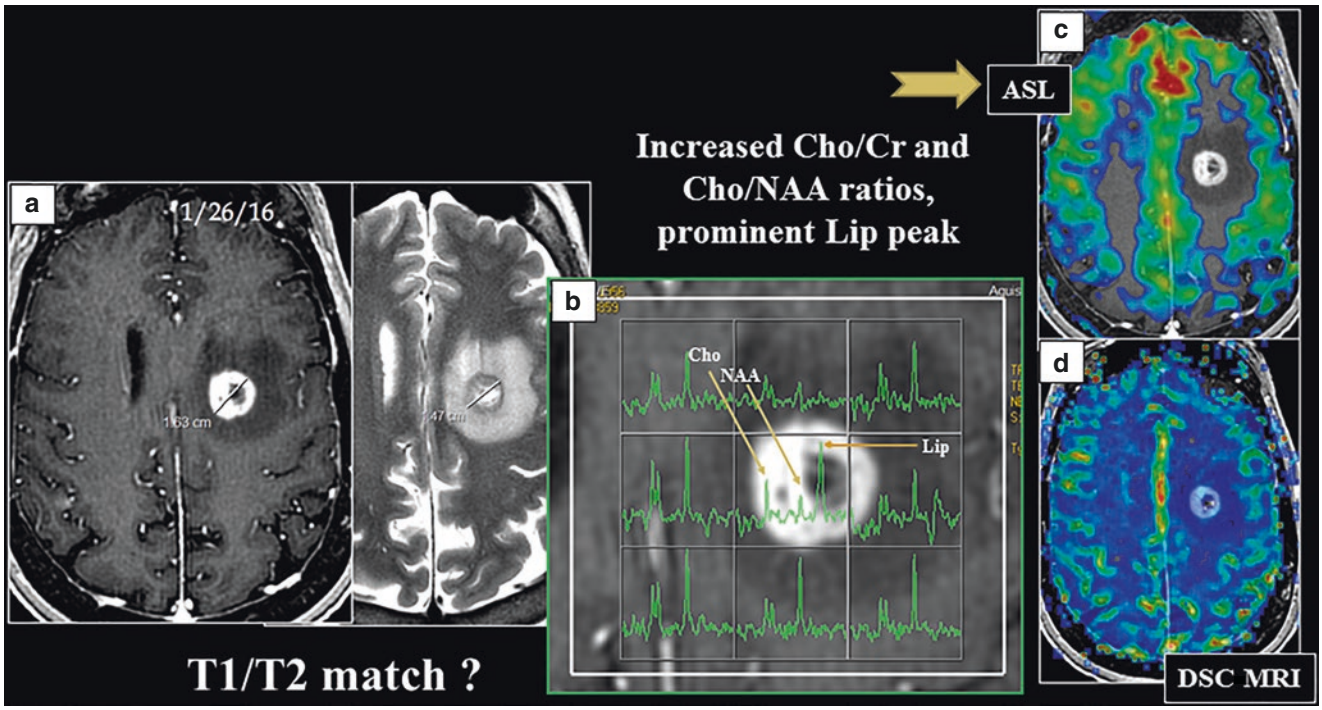

Fig. 4 Crucial role of perfusion-weighted imaging in differentiating radiation-induced necrosis from tumor progression in a complicated clinical case of a contrast-enhanced lesion enlarged at 7 months after Gamma Knife radiosurgery. Conventional magnetic resonance imaging (MRI) (**a**) showed ambiguous results with a doubtful T1/T2 match. Proton magnetic resonance spectroscopy (**b**) revealed elevated choline/creatinine (Cho/Cr) and choline/N-acetyl aspartate (Cho/NAA) ratios in the presence of a prominent lipid (Lip) peak (such changes may suggest tumor progression, but early radiation-induced necrosis rather often also demonstrates spuriously increased Cho content). Nevertheless, both arterial spin labeling (ASL) and first-pass dynamic susceptibility-weighted contrast-enhanced (DSC) MRI (**c** and **d**, respectively) indicated very low perfusion in the lesion, which allowed the presence of an active neoplasm to be ruled out, and this was confirmed on numerous follow up exams

ASL is based on subtraction of magnetic resonance images and does not require administration of contrast media. A pulse sequence is used to magnetically tag the hydrogens in inflowing arterial blood in a target area, and a delayed image is acquired. Thereafter, the same sequence is repeated without blood labeling, and the final subtraction composite image provides information on CBF. Perfusion parameters may be presented both qualitatively (as color-coded maps on which red and blue colors typically indicate areas with high and low CBF, respectively) and quantitatively (with positioning of the ROI in the area of interest) in millilitres per 100 g per minute. Color coding of blood flow significantly facilitates the data analysis, especially in diagnostically difficult cases. Of note, quantitative assessment of CBF with ASL is considered a highly reliable and consistently reproducible technique accompanied by a small range of data variability [3, 7–13, 15, 27, 28, 30].

Several technical and physiological parameters influence the signal obtained with ASL, including magnetization transfer effects, labeling efficiency, the T1 relaxation times of blood and soft tissue, and the arterial transit time to the segment of interest [13]. In addition, measurements of TBF may depend on the tumor size and vascularity [29]. In the present series, BM of RCC, which are known for their prominent vascularization, demonstrated increased TBF in comparison with neoplasms of other origins. Previous studies have shown that CBF is increased in early childhood and gradually decreases later to the normal adult level. Furthermore, after approximately 30 years of age, perfusion of gray matter usually demonstrates a progressive decline. It is also important to note that several other factors may influence CBF and TBF and may have an impact on their longitudinal assessment, necessitating calculation of rTBF. For example, global and regional CBF may be affected by the hematocrit value, various medications (including anticancer chemotherapeutic drugs), the presence of comorbidities (in particular, Alzheimer's disease and other dementias), and even by diet (e.g., coffee consumption) [3, 12, 13, 15].

Nevertheless, one of the main advantages of ASL in comparison with contrast-based PWI techniques is that measurement of tissue blood flow does not depend on breakdown of the BTB/BBB [3, 6, 7, 9, 12, 13]. Both DSC and dynamic contrast-enhanced (DCE) MRI are prone to erroneous results—in particular, caused by the presence of a hemorrhage, melanin deposits, cysts, or significant extravasation of the contrast media as a result of increased vessel leakiness within the investigated area. In addition, DSC MRI does not

permit absolute quantification of perfusion parameters [3, 6, 9, 12, 13]. Another advantage of ASL is the speed of the investigation, since just 2–6 min (depending on the PLD time used) is needed for its acquisition [3, 6–10, 15, 27]. In our practice, with use of a 3T MRI scanner (General Electric, Chicago, IL, USA), acquisition of pseudocontinuous ASL with dual PLD times of 1.5 and 2.5 s takes 2 min 10 s and 2 min 38 s, respectively.

The fully nonionizing and noninvasive nature of ASL allows absolute safety, which significantly facilitates its use in daily radiological practice and makes its application particularly attractive in high-risk populations such as children, the elderly, patients with renal dysfunction, and patients requiring repeat perfusion examinations (e.g., during follow-up after SRS for BM). ASL sequences are now available for most major clinical MRI platforms, and the corresponding software is usually included in standard imaging packages. Therefore, as soon as this technique is standardized, it may become a uniform tool for evaluation of TBF and CBF in patients with brain tumors, both before treatment and during subsequent follow-up. It may allow optimization of individually selected therapeutic strategies to provide the best possible outcome [30]. In addition, comprehensive clinical studies in neuro-oncology may require a reliable and reproducible method for standardized quantitative TBF and CBF measurements with low inter- and intraindividual variability, and ASL can meet this need effectively [3, 6, 7, 12, 13, 15].

Importance of Perfusion Measurements at Baseline

Elevated blood flow in an enlarging contrast-enhancing intracranial lesion after therapeutic irradiation is frequently considered a prerequisite for diagnosis of brain tumor progression, and it is widely accepted that low blood flow characterizes radiation-induced changes [10]. In 2015, Lai et al. [10] reported that the diagnostic accuracy of ASL in differentiating tumor recurrence from radiation-induced necrosis after SRS for a BM was superior to those of PET and SPECT; the specificities of the compared techniques were 100%, 75%, and 62.5%, respectively. However, in that study, the perfusion parameters of the neoplasm before treatment were not taken into consideration (Dr. Clark C. Chen 2016, personal communication).

The results presented herein indicate that at baseline, approximately 40% of BM have TBF lesser than or equivalent to CBF in the healthy contralateral cerebral cortex, and it is most likely that their possible recurrence after SRS will not be accompanied by an increase in blood flow as well. Therefore, in such cases, ASL (as well as other PWI techniques) may have insufficient sensitivity for identification of tumor regrowth and will be accompanied by a high rate of false negative results. This should be borne in mind for avoidance of diagnostic errors resulting in an inappropriate treatment strategy with a negative impact on the patient's prognosis. Investigation of TBF before treatment may allow recognition of such cases in advance; thus, alternative diagnostic modalities beside PWI may be applied as necessary to rule out tumor recurrence.

Conclusion

For avoidance of diagnostic errors during PWI-based differentiation of radiation-induced effects from regrowth of a BM, it may be advisable to perform TBF measurements in all patients at baseline before SRS. For this purpose, application of ASL seems most reasonable in view of its speed, noninvasiveness, safety, reproducibility, and ready availability. It can be expected that routine inclusion of this technique in standard multimodality imaging of patients with brain tumors, both before treatment and during follow-up, will allow important complementary diagnostic information to be obtained. Nevertheless, validation of the clinical efficacy of such a diagnostic strategy and a cost/benefit analysis of it should be done in further studies involving large numbers of patients.

Conflict of Interest The authors have no conflict of interest concerning the reported materials or methods.

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Gamma Knife Radiosurgery for Symptomatic Cavernous Malformations: Tokyo Women's Medical University Experience

Ayaka Sasaki, Motohiro Hayashi, Noriko Tamura, Ayako Horiba, and Takakazu Kawamata

Abstract *Objective:* This retrospective study evaluated the results of Gamma Knife surgery (GKS) for symptomatic cavernous malformations (CM) of the brain.

Methods: From 1993 till 2014, 11 patients (mean age 44 years) with a symptomatic CM underwent GKS at Tokyo Women's Medical University. In six cases, the disease manifested with hemorrhaging. Seizures and a neurological deficit were noted in four patients each. The CM were located in the brainstem (in 5 cases), basal ganglia (in 2 cases), thalamus (in 2 cases), and cerebral lobe (in 2 cases). The mean lesion volume was 1.46 cc. The mean marginal dose was 15.3 Gy. The mean length of follow-up after GKS was 78.5 months.

Results: At the last follow-up, the general status was considered excellent, fair, and poor in 8 patients (73%), 1 patient (9%), and 2 patients (18%), respectively. The annual hemorrhage rates per case-year were 2.94% from birth till GKS, 20.20% from the first hemorrhage till GKS, 4.54% within the first 2 years after GKS, and 1.39% within the entire follow-up period after GKS. Two patients attained seizure-free status after treatment.

Conclusion: GKS may be considered as a possible management option for symptomatic CM, since it reduces the subsequent hemorrhage risk after the initial bleeding episode. Moreover, in some patients, cessation of symptomatic epilepsy after treatment may be expected.

A. Sasaki · N. Tamura · A. Horiba · T. Kawamata
Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

M. Hayashi (✉)
Faculty of Advanced Techno-Surgery and Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

Saitama Gamma Knife Center, Sanai Hospital, Saitama, Japan
e-mail: gkrmoto@gmail.com

Keywords Annual hemorrhage rate · Gamma Knife radiosurgery · Hemorrhage-free survival · Seizure control Symptomatic cavernous malformation

Introduction

Cavernous malformations (CM) of the central nervous system are congenital anomalies, whose recognition has grown in parallel with progress in the availability of diagnostic MRI. These lesions can be located in any brain region, and, according to imaging-based studies, their incidence varies from 0.4% to 0.8% [1–4]. Pathologically, CM are considered capillary dysplasia and appear as dilated vascular channels lined by epithelial and fibrous walls without brain parenchyma in between [2, 5]. The vast majority of CM remain clinically asymptomatic throughout life, but some of them behave aggressively and manifest with hemorrhaging, seizures, and/or a focal neurological deficit [1–3, 6, 7]. Magnetic resonance imaging (MRI) is the method of choice used for their diagnosis in both incidental and symptomatic cases.

Management of brain CM remains controversial. According to the *Japanese Guidelines for the Management of Stroke* (2015) [8], treatment is recommended only for symptomatic CM. The indications for stereotactic radiosurgery in such cases are usually limited to surgically inaccessible lesions. Nevertheless, a nationwide study in Japan did not reveal a significant difference in hemorrhage-free survival in patients with CM treated with surgery versus those treated with radiosurgery [9]. The objective of the present retrospective study was evaluation of the results of Gamma

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*,
Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_13,

Knife surgery (GKS) in patients with symptomatic CM who underwent treatment at Tokyo Women's Medical University.

Materials and Methods

Between 1993 and 2014, 11 patients with symptomatic CM underwent GKS at our clinic. Their medical records and radiological data were reviewed, with an emphasis on the clinical course after treatment, including the general and neurological status, annual hemorrhage rates (AHR), and seizure control.

There were 4 men and 7 women aged from 29 to 66 years (mean age 44 years). In 6 patients, the disease manifested with hemorrhaging, which happened once (in 3 cases), twice (in 2 cases), or multiple times (in 1 case). Seizures and a neurological deficit were noted in 4 patients each. In all cases, the diagnosis was established with MRI. The CM were located in the brainstem (in 5 cases), basal ganglia (in 2 cases), thalamus (in 2 cases), and cerebral lobe (in 2 cases). The lesion volume at the time of GKS ranged from 0.5 to 3.7 cc (mean 1.46 cc). Radiosurgical planning and radiation dosimetry were done with Leksell GammaPlan® (Elekta AB; Stockholm, Sweden), and treatment was performed by means of Leksell Gamma Knife models B, C, and Perfexion™ (Elekta AB). The marginal dose varied from 8 to 24 Gy (mean 15.3 Gy).

Results

During follow-up after GKS (mean 78.5 months), no patient died. At the time of the last clinical examination, the general status was considered excellent, fair, and poor in 8 patients (73%), 1 patient (9%), and 2 patients (18%), respectively. After treatment, 2 patients experienced seizures, whereas involuntary movements, worsening of headaches, a neurological deficit, and hemorrhaging were noted in 1 patient each.

Annual Hemorrhage Rates

In the present series, the AHR from birth till GKS was 2.94% per case-year, and from the first hemorrhage till GKS, it was 20.20% per case-year. After treatment, the AHR were 4.54% per case-year within the first 2 years of follow-up and 1.39% per case-year within the entire follow-up period.

Seizure Control

All four patients who presented with seizures before GKS continued use of their antiepileptic drugs (AED) after treatment. In two of them, both of whom had experienced previous hemorrhaging, no seizures had occurred by the time of the last follow-up, whereas in two others, both of whom had not experienced previous hemorrhaging, a significant reduction in seizure frequency was noted.

Illustrative Cases

Case 1

A 38-year-old woman visited our hospital, complaining of a headache, which, as she noted, had appeared for the second time in her life. T2-weighted MRI demonstrated a pontine lesion with high signal intensity in the center and low signal intensity at the periphery (Fig. 1), consistent with the diagnosis of a hemorrhagic CM. Six months later, the patient underwent GKS. During 4-year follow-up after treatment, she was in excellent general condition without any neurological deficit.

Case 2

A 50-year-old woman presented after a seizure, and MRI revealed a hemorrhagic CM in the left frontal lobe. Two months after her diagnosis, she underwent GKS with a marginal dose of 19 Gy delivered to the 60% isodose line (Fig. 2). T2-weighted MRI at 1, 6, and 11 years after treatment consistently demonstrated a residual lesion surrounded by prominent perifocal edema. After GKS, the patient consistently used an AED and never experienced any repeated seizures.

Discussion

Clinical decision-making in cases of a symptomatic CM should always consider whether the selected treatment option really carries greater advantages over pure observation (i.e., the natural history of the disease).

The reported AHR of CM have ranged widely from 0.7% to 6.0% per case-year, but it is generally accepted that

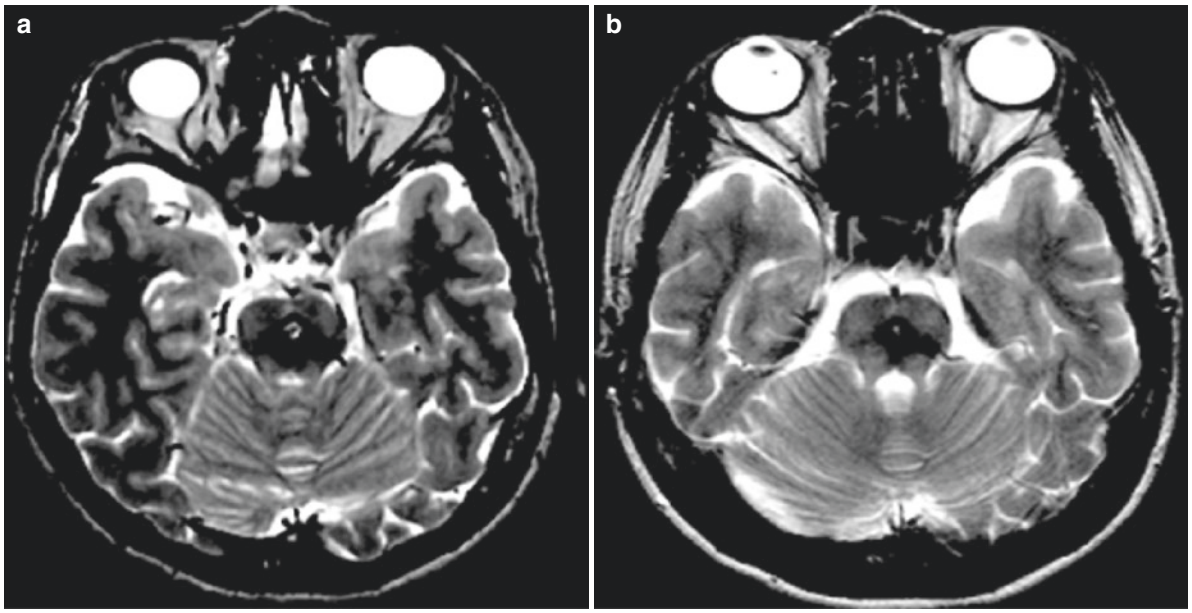

Fig. 1 T2-weighted magnetic resonance imaging at the time of diagnosis (**a**) and 4 years after Gamma Knife radiosurgery (**b**) for a hemorrhagic pontine cavernous malformation in a 38-year-old woman with a recurrent headache

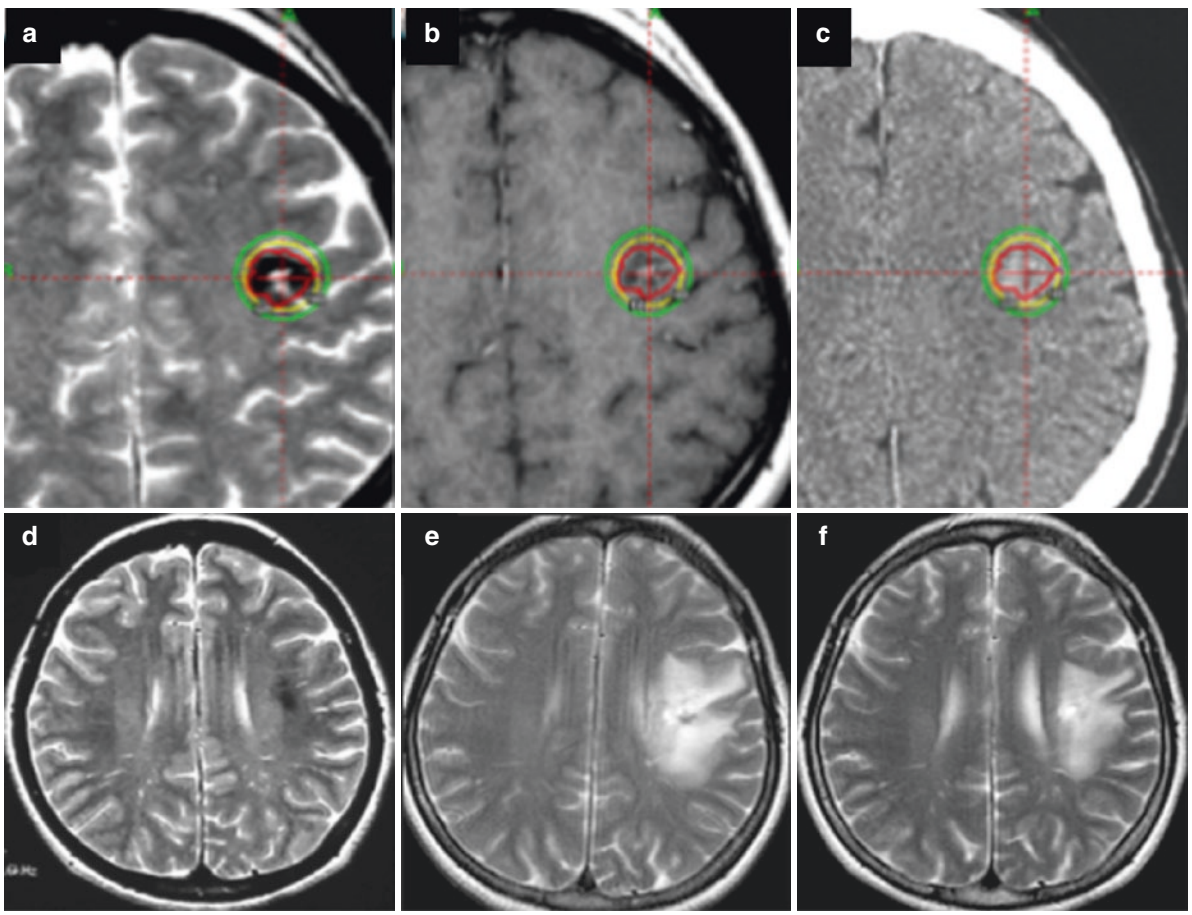

Fig. 2 Treatment plan for Gamma Knife radiosurgery of a hemorrhagic cavernous malformation in the left frontal lobe in a 50-year-old woman who presented with a seizure (**a**–**c**), and follow-up T2-weighted magnetic resonance imaging at 1 year (**d**), 6 years (**e**), and 11 years (**f**) after treatment, demonstrating a residual lesion surrounded by prominent perifocal edema

after the first bleeding episode, the patient has a higher subsequent hemorrhage risk [10]. Indeed, the reported AHR in cases without and with prior hemorrhaging have been 0.6% and 4.5% per case-year, respectively [10]. Consistent with these rates, in the present series, the AHR from birth till GKS was 2.94% per case-year, but it rose to 20.20% within the time interval from the first hemorrhage till GKS. The question is whether radiosurgery contributes to a reduction in the subsequent hemorrhage risk in such cases. Several reports [1, 2, 4, 10], including a multi-institutional retrospective study in Japan [9], have indicated that it really does, and they have shown that in comparison with the time interval from the first hemorrhage till radiosurgery, the AHR undergoes a prominent reduction after treatment. Our results presented herein corroborate the previous findings (Table 1) and provide additional support for use of GKS in patients with hemorrhagic CM for improvement of the clinical course of the disease through prevention of repeat hemorrhaging.

Another question is whether the prevention of subsequent hemorrhaging provided by GKS is comparable to that observed after microsurgery. The latter is widely considered the best option for avoidance of repeat hemorrhaging as soon as complete resection of the lesion is attained. However, incomplete removal, which is not very uncommon in cases of an eloquently located CM, does not reduce the AHR in comparison with conservative treatment [11]. Moreover, resection of a symptomatic CM located in the brainstem or basal ganglia is risky and may result in major postoperative morbidity. On the other hand, conservative management in such cases is not very effective. For example, in the series reported by Garrett and Spetzler [12], out of 14 observed patients with a brainstem CM, 7 (50%) either improved or were stable, 4 (29%) deteriorated, and 1 (7%) died. At the same time, Kida et al. [9] noted comparable hemorrhage-free survival after radiosurgery and surgery for CM.

Table 1 Annual hemorrhage rates in radiosurgery-treated patients with hemorrhagic cavernous malformations of the brain

	Annual hemorrhage rate (% per case-year)		
Time interval	Present series	Multi-institutional retrospective study in Japan [9]	Other series [1, 2, 4, 10]
From birth till SRS	2.94	3.9	2.0–6.4
From the first hemorrhage till SRS	20.20	21.4	7.3–22.4
Within the first 2 years after SRS	4.54	7.4	7.1–14
Within the entire follow-up period after SRS	1.39	4.4	0.8–5.2

SRS stereotactic radiosurgery

The annual seizure rates in patients with CM range from 1.5% to 4.3% but are higher (up to 5.5%) in those individuals who have previously had seizures [1, 4]. According to Fernández et al. [13], at least in cases of non-refractory symptomatic epilepsy, lesion resection does not lead to a significant improvement in postoperative seizure control in comparison with conservative treatment. Still, there are no data showing that GKS provides better seizure control than other treatment options. However, the pathophysiology of seizures may play a role. Kida et al. [9] defined two types of symptomatic epilepsy causes in cases of CM: (1) repetitive minor hemorrhages and (2) hemosiderin deposition in the perilesional brain tissue without clinically recognizable hemorrhaging. The former type may be more amenable to seizure control after radiosurgery, while the latter one may be associated with resistance of symptomatic epilepsy to such treatment. Of note, two patients in our series, who presented with seizures and had experienced hemorrhaging, attained seizure-free status after GKS and were in excellent general condition at the time of the last follow-up.

Conclusion

Surgery should be considered the method of choice for management of a symptomatic CM if the lesion can be resected completely and safely. Nevertheless, GKS may be an alternative treatment option, since it reduces the subsequent hemorrhage risk after the initial hemorrhage. Moreover, in patients who present with seizures and experience hemorrhaging, cessation of symptomatic epilepsy after GKS may be expected. Corroborating previous reports, the results from Tokyo Women's Medical University indicate that GKS may provide greater advantages for patients with a symptomatic CM than conservative treatment. Careful selection of the most suitable candidates and appropriate timing of radiosurgery are important prerequisites for attainment of the best possible outcome.

Conflict of Interest The authors have no conflict of interest concerning the reported materials or methods.

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Gamma Knife Thalamotomy for a Medically Refractory Tremors: Longitudinal Evaluation of Clinical Effects and MRI Response Patterns

Taku Ochiai

Abstract *Objective:* The present longitudinal study evaluated the results of Gamma Knife surgery (GKS) for medically refractory tremors.

Methods: The outcome after Gamma Knife thalamotomy targeting the ventral intermediate nucleus (VIM) was analyzed in 17 patients (9 men and 8 women; mean age 72 years) with either Parkinson's disease or an essential tremor, who were followed up for at least 2 years after treatment. Clinical and magnetic resonance imaging (MRI) examinations were done before and every 3 months after GKS.

Results: The mean rates of symptom improvement (a decrease in the tremor frequency) were 6%, 39%, 63%, and 64% at 3, 6, 12, and 24 months after treatment, respectively. The defined MRI response patterns included a minimum reaction (in 3 patients), a normal reaction (in 11 patients), and a hyperreaction (in 3 patients). They were not associated with any evaluated pretreatment, radiosurgical, or outcome parameter, although 2 patients with a hyperreaction exhibited mild-to-moderate motor weakness in the contralateral limbs. Linear contrasting of the border between the thalamus and the internal capsule adjacent to the lesion site was noted on follow-up MRI in 13 cases and was associated with a higher symptom improvement rate.

Conclusion: GKS allows effective and safe management of medically refractory tremors. The treatment is characterized by variable MRI response patterns. Some imaging findings during follow-up may be associated with clinical effects.

T. Ochiai (✉)
Ochiai Neurological Clinic, Saitama, Japan
e-mail: ochiait@me.com

Keywords Essential tremor · Functional radiosurgery Gamma Knife radiosurgery · Gamma Knife thalamotomy Movement disorders · Parkinson's disease · Ventral intermediate nucleus

Introduction

Gamma Knife surgery (GKS) is a type of stereotactic radiosurgery that allows for very precise high-dose irradiation of selected intracranial target(s). At present, it is widely used for management of a variety of intracranial pathological conditions, including benign and malignant tumors and vascular malformations. The first experience with application of GKS for thalamotomy in a patient with intractable pain dates back to 1967 [1]. Nowadays, this modality is widely utilized for functional indications. The present study was directed at longitudinal evaluation of clinical effects and radiological response patterns after GKS for medically refractory tremors in patients who were followed up for at least 2 years after treatment.

Patients and Methods

Between 2004 and 2014, 26 patients underwent Gamma Knife thalamotomy targeting the ventral intermediate nucleus (VIM) for management of medically refractory tremors at our clinic, and 17 of them were followed up for at least 2 years thereafter in compliance with the standard follow-up protocol. The latter group comprised the study cohort for the present analysis. There were 9 men and 8 women (mean age 72 years), each of whom had either Parkinson's disease (8 cases) or an essential tremor (9 cases). The mean time interval from the onset of the tremor until treatment was 10 years.

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*,
Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_14,

Radiosurgical Technique

The details of target selection and radiosurgery treatment planning have been highlighted previously [2]. Briefly, GKS was done on an outpatient basis, using Leksell Gamma Knife model 4C or Gamma Knife Perfexion™ (Elekta AB; Stockholm, Sweden) in 15 and 2 cases, respectively. As in standard targeting techniques for radiofrequency thalamotomy and deep brain stimulation (DBS), the location of the VIM for Gamma Knife thalamotomy was primarily determined according to the Schaltenbrand–Wahren atlas (3 mm above the anterior commissure–posterior commissure (AC-PC) line, 16 mm lateral from the midline, and 4 mm posterior from the midpoint of the AC-PC line) and was further adjusted with regard to the size of the third ventricle and the entire brain [2, 3]. In all cases, one 4 mm isocenter was used with delivery of a maximum radiation dose of 130 Gy. Plugging for avoidance of extreme irradiation of the internal capsule was applied in 8 cases. The mean irradiation time during the treatment was 74 min.

Clinical and Radiological Evaluations

Both before and every 3 months after GKS, all patients underwent videotaping of a tremor in the dominant upper limb with calculation of its frequency per 10 sec (measured in decihertz (dHz)) and radiological examination with plain T1- and T2-weighted magnetic resonance imaging (MRI). For the current longitudinal analysis, data obtained at 3, 6, 12, and 24 months after treatment were used.

Results

Symptomatic improvement (a decrease in the tremor frequency) was initially noted at 3 months after Gamma Knife thalamotomy and had significantly progressed by 12-month follow-up but mostly plateaued thereafter, with only a slight further advance by 24-month follow-up (Fig. 1). In one patient, after initial improvement, mild exacerbation of the symptoms was noted within the interval from 12 to 24 months after treatment, but the tremor frequency at 24-month follow-up was still lower than that before GKS (the tremor frequencies were 37 dHz and 42 dHz, respectively; symptom improvement rate 12%).

The mean symptom improvement rates were 6%, 39%, 63%, and 64% at 3, 6, 12, and 24 months, respectively. At 3 months after treatment, the vast majority of patients (77%) did not demonstrate any changes in symptoms or had only a minimal (<10%) decrease in the tremor frequency. However, at 6-month follow-up, a ≥10% decrease in the tremor frequency was revealed in 82% of patients, whereas at 12 months and 24 months after treatment, a ≥50% decrease

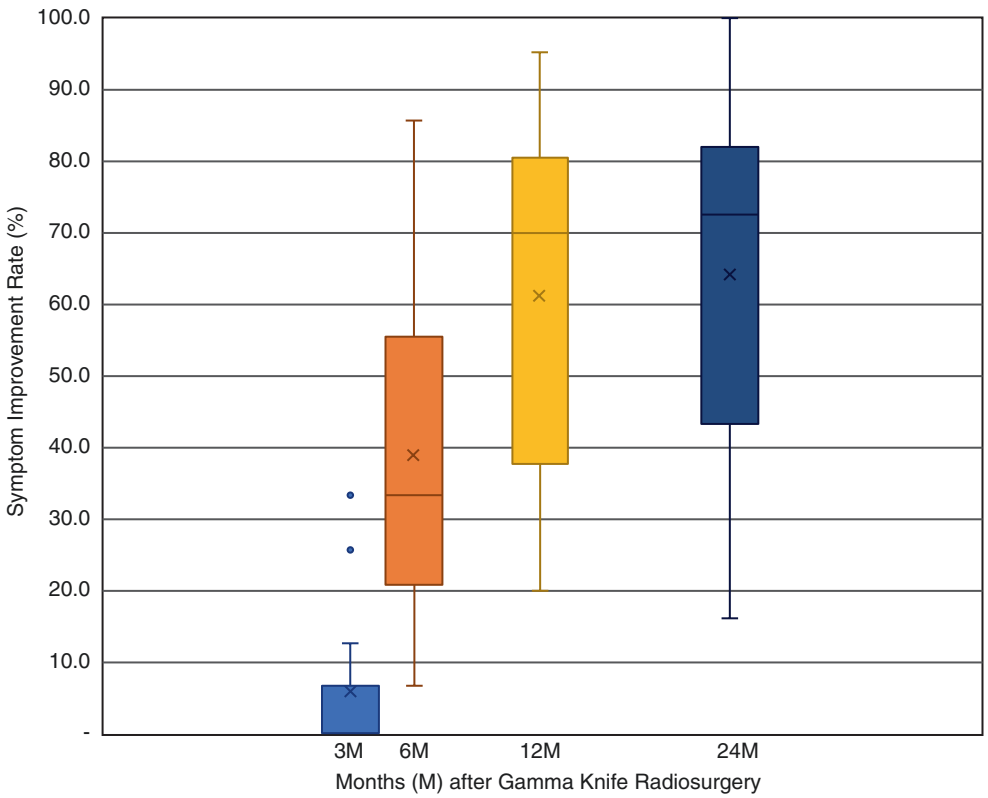

Fig. 1 Rates of symptom improvement (a decrease in the tremor frequency) after Gamma Knife thalamotomy in the present series. The mean values are defined by *crosses* and the median values by *horizontal bars* within the *box plots*

in the tremor frequency was noted in 71% and 77% of patients, respectively.

Patients demonstrating a ≥10% decrease in the tremor frequency at 3 months after Gamma Knife thalamotomy showed high rates of symptomatic improvement at 24-month follow-up (mean symptom improvement rate 80%). In contrast, patients demonstrating a <20% decrease in the tremor frequency at 6 months after treatment showed low rates of symptomatic improvement at 24 months (mean symptom improvement rate 31%).

There was no statistically significant difference in symptom improvement rates between patients with Parkinson's disease and those with an essential tremor (mean improvement rates 67% versus 62%).

MRI Response Patterns

Signal changes in the target area were observed on MRI in 35%, 88%, and 100% of patients at 3, 6, and 12 months after Gamma Knife thalamotomy, respectively. In 13 patients (77%), signal changes showed further progression by 24-month follow-up. In 3 patients (18%), an attenuation in signal changes was noted between 18 and 24 months after treatment.

Three types of radiological response patterns were defined on T2-weighted MRI (Fig. 2) [2]. A minimum reaction—characterized by minimal signal changes in the target area and absent or very limited adjacent brain edema at 12 and 24 months after treatment—was noted in 3 patients (18%). A normal reaction—characterized by a hyperintense signal at the target and in the adjacent area, demonstrating progression and a trend toward convergence by 24-month follow-up but affecting the thalamus only partly—was noted in 11 patients (64%). A hyperreaction—characterized by a prominent hyperintense signal appearing early (by 6 months) after treatment and demonstrating further progression (usually without a trend toward convergence) by 24-month follow-up, with occasional involvement of the entire thalamus—was noted in 3 patients (18%). There was no association between development of defined radiological response patterns and any evaluated pretreatment or radiosurgical parameter.

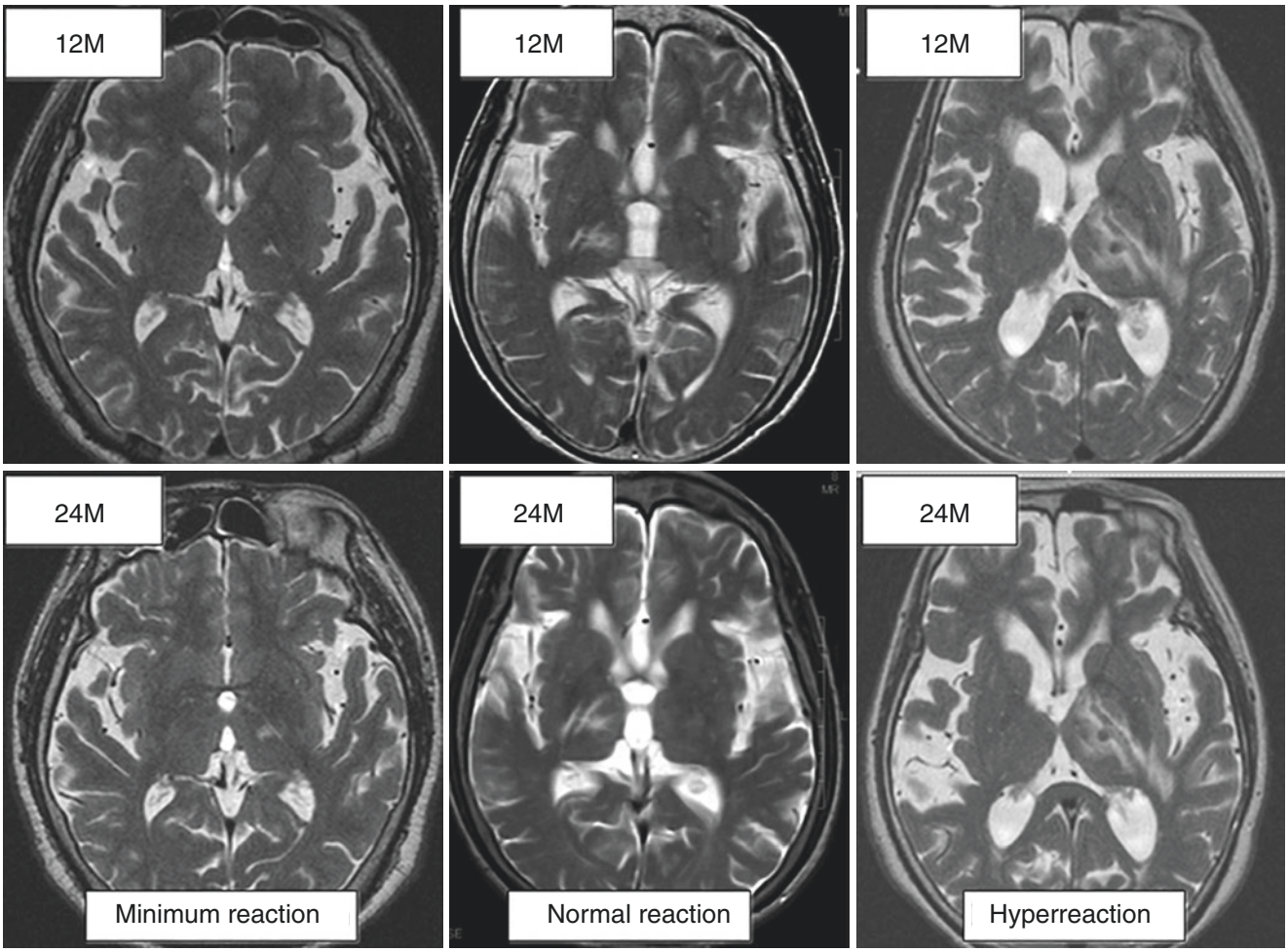

Fig. 2 Defined types of radiological response pattern on T2-weighted magnetic resonance imaging at 12- and 24-month (M) follow-up after Gamma Knife thalamotomy: minimum reaction (left), normal reaction (center), and hyperreaction (right). Note the linear contrasting of the border between the thalamus and the internal capsule adjacent to the lesion site

In addition, during the course of follow-up, 13 patients (77%) showed linear contrasting of the border between the thalamus and the internal capsule adjacent to the lesion site, and in 12 of them, such a radiological finding was present at 24-month MRI examination.

Associations Between MRI Response Patterns and Clinical Effects

The type of radiological response pattern on T2-weighted MRI and the speed of imaging change development were not associated with the symptom improvement rate. However, in patients who demonstrated posttreatment linear contrasting of the border between the thalamus and the internal capsule adjacent to the lesion site, the symptom improvement rate was higher than that in individuals in whom such a radiological finding was not identified (mean 73% versus 46%).

Complications

Two patients (12%) exhibited mild-to-moderate motor weakness in the contralateral limbs after GKS. In one of them, early signal changes on MRI were marked at 3 months after Gamma Knife thalamotomy and a neurological deficit appeared at 12 months after treatment, by which time, radiation-induced brain edema, spreading across the entire thalamus (a hyperreaction), was noted. During subsequent follow-up at up to 24 months after irradiation, the brain edema regressed, and this was accompanied by an improvement in motor function. In another patient, the initial signal changes on MRI were marked at 6 months after Gamma Knife thalamotomy and a neurological deficit appeared at 24 months after treatment, by which time, the presence of small cystic lesion in the target area was suspected and radiation-induced brain edema spreading across the entire thalamus (a hyperreaction) was noted.

Discussion

Stereotactic neurosurgery for management of tremors was widely introduced into clinical practice in the 1950s [4]. Starting from the end of the 1990s, the primarily used technique of radiofrequency thalamotomy was largely replaced by the less invasive method of DBS [5]. Moreover, contemporary development of such advanced medical technologies as GKS and transcranial MR-guided focused ultrasound (TcMRgFUS) has provided an opportunity for practically noninvasive ablation therapy for functional brain disorders. On any occasion, the most commonly used target for management of a tremor is the VIM of the thalamus, whose cells may act as tremorigenic pacemakers [5]. The VIM receives output from the cerebellum via the cerebellothalamic tract passing through and anteriorly to the red nucleus. The latter is a part of the Guillain–Mollaret triangle (also known as the myoclonic triangle or the dentate-rubro-olivary tract), which also comprises the inferior olivary nucleus, the contralateral dentate nucleus, and their interconnections. Dysfunction of this circuit is currently considered the main underlying mechanism of a tremor [6].

The effectiveness of Gamma Knife thalamotomy targeting the VIM in cases of a medically refractory tremor was highlighted in several previous reports, demonstrating approximately 80% symptomatic improvement [2, 3, 7–12]. In concordance, in the present study, the mean symptom improvement rate at 2 years after treatment was 64% and a ≥50% decrease in the tremor frequency was noted in 77% of cases. Moreover, in patients who demonstrated early response (with a ≥10% decrease in the tremor frequency at 3 months after GKS), the mean symptom improvement rate at 24 months after treatment was 80%. This indicates that the effectiveness of GKS for management of a tremor may be comparable to those of other neurosurgical modalities (such as, radiofrequency thalamotomy and DBS).

Mathieu et al. [13] reported symptom recurrence in 2 out of 6 patients (33%) who underwent Gamma Knife thalamotomy for a tremor caused by multiple sclerosis. In our series, one patient (6%), after initial improvement, showed a mild exacerbation of symptoms within the second posttreatment year, but the tremor frequency at 24-month follow-up was still lower than that before GKS; thus, even in this case, the applied treatment could be considered effective.

Signal changes in the target area observed on MRI after Gamma Knife thalamotomy vary in terms of their timing and development patterns, which may reflect individual differences in radiation sensitivity. In many cases, imaging findings appeared nearly simultaneously with an initial decrease in the tremor frequency. In the majority of patients, signal changes on MRI showed progression until the 24-month follow-up examination, and only in a few cases was attenuation of hyperintensity noted during this time interval. This indicates that regular radiological examinations should preferably be done for at least 2 years (or for even longer) after Gamma Knife thalamotomy (Fig. 3).

In comparison with DBS and thalamotomy (by means of either radiofrequency thermocoagulation or TcMRgFUS), which provide an immediate result, the clinical effects of GKS on tremors are delayed by 3–6 months, and prediction of treatment efficacy on the basis of clinical and radiosurgical

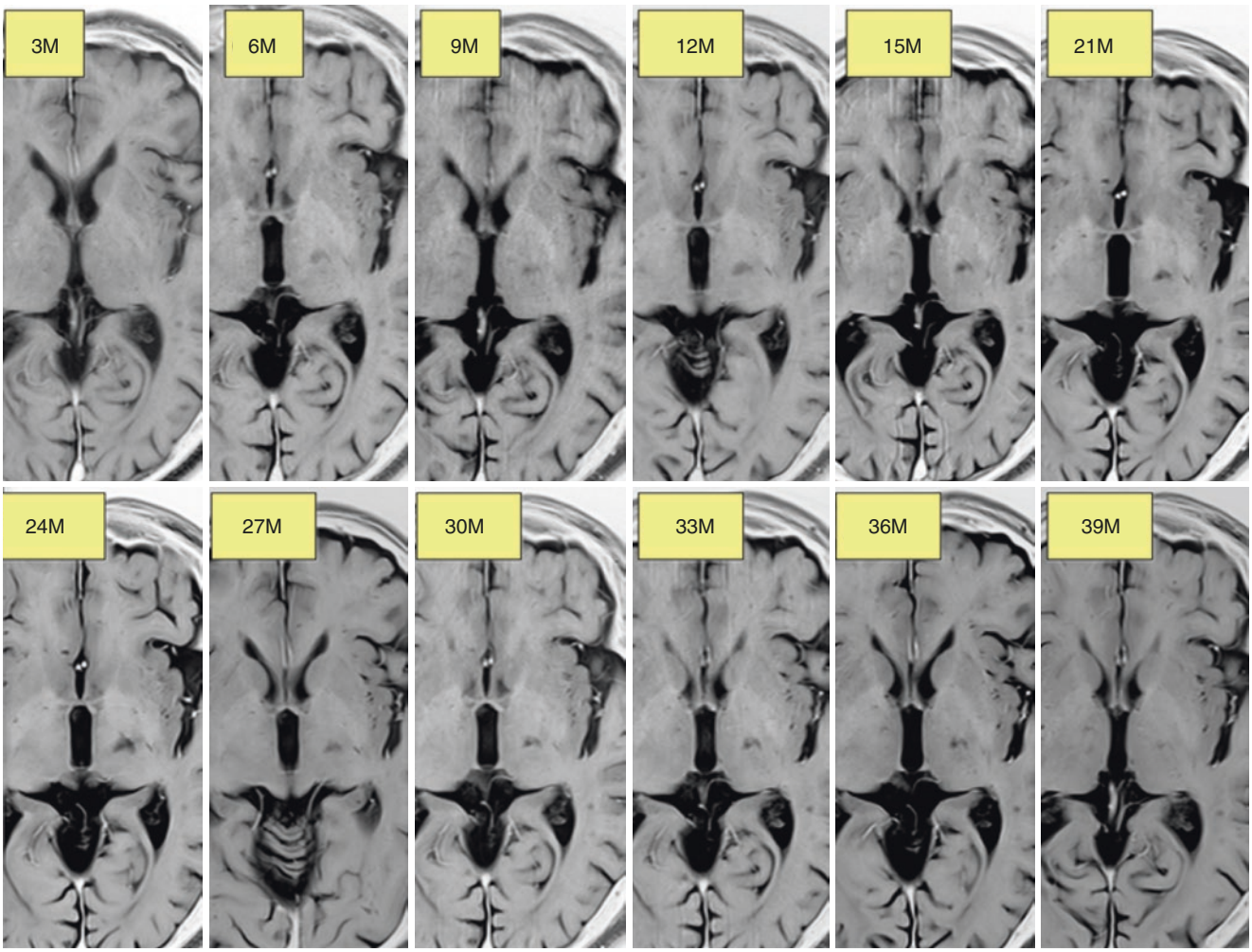

Fig. 3 Longitudinal magnetic resonance imaging examinations after Gamma Knife thalamotomy for essential tremor, targeting the left ventral intermediate nucleus (a normal reaction pattern). The initial signal changes in the target area appeared 6 months (M) after treatment, whereas the linear contrasting of the border between the thalamus and the internal capsule adjacent to the lesion site became clearly visible at 15 months and had further progressed by 24-month follow-up. These changes gradually converged and attenuated during subsequent observation

factors is nearly impossible. However, longitudinal evaluation of imaging characteristics may be somewhat helpful. Defined radiological response patterns, mainly reflecting the extension and time course of the perilesional edema, could not be predicted before treatment and did not show any association with symptom improvement rates, while both patients exhibiting complications (motor weakness in the contralateral limbs) demonstrated a hyperreaction on MRI. At the same time, the presence of linear contrasting of the border between the thalamus and the internal capsule adjacent to the lesion site was associated with higher symptom improvement rates, which may have reflected the appropriateness of treatment planning and its positive impact on clinical outcome. The prognostic value of this imaging finding may be helpful during evaluation of patients after Gamma Knife thalamotomy and for prediction of treatment effectiveness.

Conclusion

Gamma Knife thalamotomy targeting the VIM allows effective and safe management of medically refractory tremors, and its clinical efficacy may be comparable to those of more invasive stereotactic techniques (i.e., radiofrequency thalamotomy and DBS). GKS is characterized by variable radiological response patterns, which, however, are not associated with symptom improvement rates, while some imaging findings on follow-up MRI may be predictive of clinical effects. Despite its recognized limitations (e.g., unilateral treatment and a delayed response to treatment), Gamma Knife thalamotomy may be considered useful in medically fragile patients with systemic comorbidities, as well as in individuals who are reluctant to undergo invasive surgical procedures.

Conflict of Interest The author has no conflict of interest concerning the reported materials or methods.

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Pituitary Radiosurgery for Management of Intractable Pain: Tokyo Women's Medical University Experience and Literature Review

Mikhail F. Chernov and Motohiro Hayashi

Abstract Surgical or chemical hypophysectomy has historically shown good effectiveness in management of intractable pain but has often been accompanied by serious complications. In contrast, high-dose irradiation of the pituitary gland and stalk provides comparable analgesic effects and is associated with minimal morbidity. Although its physiological mechanism remains elusive, pituitary radiosurgery using the Gamma Knife has demonstrated high clinical efficacy and safety in cases of both cancer pain and noncancer pain. According to the available data, this treatment provides at least a temporary analgesic effect in >80% of patients, usually within hours to days after the procedure. Although the pain relief is most prominent and durable in cases of metastatic bone disease, it is not limited to that pathological condition or to cases of hormone-dependent cancers. Nevertheless, the low-quality studies reported to date cannot support any meaningful clinical recommendations on use of pituitary radiosurgery. Therefore, additional well-elaborated clinical and basic investigations, preferably performed in a multi-institutional and prospective fashion, are clearly needed and may bolster further developments of this highly promising treatment modality.

Keywords Analgesic effects · Cancer pain · Gamma Knife radiosurgery · Hypophysectomy · Malignant visceral pain Metastatic bone disease · Outcome · Pain management Physiological mechanisms · Pituitary radiosurgery Poststroke thalamic pain

M. F. Chernov
Faculty of Advanced Techno-Surgery and Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

M. Hayashi (✉)
Faculty of Advanced Techno-Surgery and Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

Saitama Gamma Knife Center, Sanai Hospital, Saitama, Japan
e-mail: gkrmoto@gmail.com

Introduction

Surgical hypophysectomy for management of intractable pain caused by metastatic breast cancer was introduced in 1953 by Luft and Olivecrona [1] and quickly attracted widespread attention from others [2–5]. Subsequently, less-invasive modifications of this technique were developed, including chemical hypophysectomy based on local injection of alcohol [6–11], implantation of radioactive isotopes into the sellar [12], and radiofrequency ablation of the pituitary gland [13]. Clinical applications of such treatments have reportedly resulted in pain relief in 40–100% of patients but have frequently been accompanied by major complications, including panhypopituitarism, diabetes insipidus, meningitis, visual dysfunction, and hypothalamic infarction.

Hypophysectomy by means of external irradiation of the sella was pioneered by Levy et al. [14, 15]. Between 1954 and 1972, their group treated 183 patients with stereotactic delivery of protons or helium ions to the pituitary gland for the purposes of its ablation and hormonal suppression in order to control the progression of metastasized breast carcinoma. The total dose (180–220 Gy) was given in 3–8 fractions [14, 15]. In the same way, starting in the 1960s, fractionated and single-session sellar irradiation treatments with protons for management of disseminated hormone-dependent cancers were utilized at dedicated centers in the USA [16] and the USSR [17–20]. Several hundred patients underwent such treatment (e.g., the Moscow series alone reportedly included 581 cases of metastatic breast and prostate carcinomas [15]), and many of them experienced long-term remission and prominent pain relief, while the rate and severity of complications were low [14–21].

Introduction of the Leksell Gamma Knife (Elekta AB; Stockholm, Sweden) into clinical practice in 1968 stimulated further interest in utilization of stereotactic radiosurgery (SRS) for therapeutic irradiation of the sella. The initial series of 762 patients treated at Sophiahemmet Hospital and Karolinska University between 1968 and 1982 included 24

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*, Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_15,

cases of radiosurgical hypophysectomy, and the primary goal of these procedures was pituitary ablation in cases of hormone-dependent cancers [22–24]. High clinical effectiveness and minimal morbidity associated with such a technique in patients with intractable pain caused by bone metastases of breast carcinoma were initially demonstrated by Backlund et al. [22, 23] and later on by Liscák and Vladyka [25]. At Tokyo Women's Medical University, pituitary radiosurgery for management of cancer pain was first applied in 2002 [26]. Herein, we review our experience with clinical use of this highly promising treatment modality, in the context of other related reports, and discuss its possible developments in the future.

Physiological Mechanisms of Hypophysectomy for Management of Pain

The physiological mechanism of hypophysectomy for management of pain remains elusive and does not appear to be related to posttreatment falls in pituitary hormone levels [10, 11, 27, 28]. In particular, an analgesic effect is usually observed within hours or days after pituitary radiosurgery, whereas associated endocrinological abnormalities inconsistently appear several months later in fewer than half of the treated patients [29]. There is some evidence that hypophysectomy may increase the concentrations of β-endorphin and its precursor pro-opiomelanocortin in the blood and cerebrospinal fluid [10, 11, 30]. Although such biochemical alterations are usually brief and cannot explain the lasting response to treatment [5], they somehow corroborate the time-dependent fading of the analgesic effect and the steadily increasing rates of pain recurrence during medium- and long-term follow-up [29]. There is also a possibility that changes in estrogen and progesterone levels after hypophysectomy modulate nociception [21]. Meanwhile, it has been suggested that the mechanisms of surgical and radiosurgical hypophysectomy may differ from each other, and while the former is clearly destructive, the latter mainly exhibits stimulatory reactions [21, 26, 29, 31–36]. This is indirectly supported by the frequently observed rapid improvement in the patient's general condition after pituitary radiosurgery, along with increases in psychomotor activity and appetite.

Current Indications for Pituitary Radiosurgery

Pituitary radiosurgery using the Gamma Knife has mainly been performed for management of intractable pain syndromes caused by either bone metastases of solid cancers [21–23, 25, 26, 31–33, 36, 37] or thalamic stroke [29, 31–35].

Metastatic Bone Disease

Metastatic bone disease complicates a wide range of malignances. It may be found at autopsy in approximately 70% of patients who succumb to cancer—in particular, originating from the breast (73%), prostate (68%), thyroid (42%), lung (36%), and kidney (35%) [38]. Bone metastases mainly affect the axial skeleton, are associated with variable prognoses, and may be related to significant morbidity, being the most common cause of cancer-related pain [39]. The latter results from stretching of periosteum (secondary to tumor growth), bone fractures, and cytokine-mediated osteoclastic bone destruction, accompanied by nociceptive stimulation [39]. Various treatment modalities—including chemotherapy, hormonal therapy, surgical resection, percutaneous minimally invasive ablation, and local irradiation—are applied in such cases for palliative purposes but usually do not result in sufficient pain relief or they have only temporary effects. Therefore, in the vast majority of patients with metastatic bone disease, administration of analgesics is unavoidable.

The recommended World Health Organization (WHO) three-step guideline for treatment of cancer-related pain includes sequential administration of nonopioids, mild opioids, and strong opioids, as well as additional medications to calm fear and anxiety [21, 40]. Morphine represents a standard drug for management of refractory cancer pain, with clearly confirmed efficacy, but its prolonged use may result in several serious side effects, such as psychosis, paraparesis, seizures, immunosuppression, and respiratory depression [41, 42]. Moreover, the therapeutic effectiveness of opioids may be decreased in elderly patients, necessitating dose reduction because of impaired hepatic and renal function [42]. Intrathecal administration of analgesics with use of programmable pumps allows delivery of highly potent doses with minimal systemic side effects but is not without drawbacks [21, 27, 40]. Among the factors challenging such treatment systems are the high costs of their maintenance and management of related complications, the typically irreversible effects of pharmacological neuromodulation (i.e., weaning individuals off this therapy is highly problematic), and possible development of opioid-induced hyperalgesia [40]. Although various destructive neurosurgical interventions—cordotomy, thalamotomy, cingulotomy, mesencephalotomy, etc. [27, 40, 43]—can be effective in patients with cancer pain that is resistant to opioids, their use may be precluded by the patient's poor general health and risk of complications. Moreover, the analgesic effects of such procedures often fade with time [21].

In our practice, patients with metastatic bone disease are deemed suitable for pituitary radiosurgery if all previously applied methods of treatment have either failed or not resulted in adequate control of pain, necessitating administration of

opioids. However, pain response to morphine has been considered a main selection criterion, since it is presumed that the effects of pituitary radiosurgery are largely related to release of endorphins triggered by high-dose irradiation of the pituitary gland [26, 31–33]. Also, in general, we prefer to administer such treatment if the patient's Karnofsky Performance Scale (KPS) score is >40. Previous brain irradiation—in particular, involving the sellar area—by means of SRS or fractionated radiotherapy (FRT), including whole-brain radiation therapy (WBRT), is also considered a relative contraindication for pituitary radiosurgery [26, 31–33].

Disseminated Cancer Without Bone Involvement

Pituitary radiosurgery has occasionally been performed in terminally ill cancer patients with neuropathic or visceral pain in whom no other therapeutic option was feasible [21, 36, 37]. However, one should be rather cautious when defining treatment indications in such cases that are refractory to opioid therapy [37].

Poststroke Thalamic Pain

Poststroke thalamic pain, also known as Dejerine–Roussy syndrome, is a type of neuropathic central poststroke pain, which can occur after ischemic or hemorrhagic cerebrovascular accidents. It may appear in the acute or subacute stages of stroke, or it may develop with a delay of months to years. Of note, thalamic lesions of nonvascular origin may occasionally cause a similar pain syndrome. Its main clinical manifestations include hypesthesia, allodynia, hyperpathia, and loss of pinprick and temperature sensations. It typically affects the contralateral side of the face, arm, and flank, but it may extend to the leg [44]. Usually, the intensity of the symptoms increases gradually. The patient suffers because severe pain may be evoked by a slight touch, by temperature or emotional changes, and even spontaneously. Various combinations of antidepressants, antiepileptic drugs, and both nonopioid and opioid analgesics are used for treatment, but their therapeutic effects are usually limited and transient. Neurosurgical options mainly include stereotactic thalamotomy or mesencephalotomy, deep brain stimulation, and motor cortex stimulation, and they have demonstrated variable success rates and different durability of pain relief [27, 44]. However, surgical treatment is frequently precluded by the presence of prominent medical comorbidity. In such cases, radiosurgical thalamotomy, usually targeting the centromedian nucleus of the thalamus, may constitute a rather effective and minimally invasive treatment option [28, 44, 45].

Alternatively, pain relief may be achieved with pituitary radiosurgery. We have applied this treatment in selected patients with disabling poststroke thalamic pain that is refractory to medical therapy, frequently at the time of symptomatic recurrence after attempted use of other neurosurgical procedures [29, 31–35]. It should be emphasized that in such cases, pain (but not numbness) should be the main complaint and disabling symptom, and, as in the scenario of metastatic cancer, at least a partial response to opioid analgesics is an important treatment selection criterion.

Pituitary Radiosurgery Treatment Planning

According to the available reports, in modern times, pituitary radiosurgery for management of intractable pain has been mainly performed using one of the various Leksell Gamma Knife models [21–23, 25, 26, 29, 31–36] or the Rotating Gamma System lnfini™ (MASEP; Shenzhen, China) [37].

Our experience at Tokyo Women's Medical University is based on use of Leksell Gamma Knife models B and C with an automatic positioning system (APS) and Perfexion™ (Elekta AB). Details of the procedure have been described in detail previously [26, 29, 31–35]. Briefly, on the day of treatment, the Leksell stereotactic frame (Elekta AB) is fixed on the patient's head and its *x* axis is arranged in parallel to the estimated position of the optic pathways. Usually, this can be done under local anesthesia, but stronger analgesia and/or sedation may be required if the pain is too severe; the same should be considered if the patient cannot tolerate a prolonged supine position during imaging before SRS and/or the treatment itself. The following plain images, with a focus on the sellar region, are obtained under stereotactic conditions: axial brain and "bone window" computed tomography (CT) (thickness 1.0 mm), axial T1-weighted magnetic resonance imaging (MRI) (thickness 1.0 mm), coronal T2-weighted MRI (thickness 2.0 mm), and axial thin-slice (thickness 0.5 mm) three-dimensional (3D) heavily T2-weighted MRI (e.g., constructive interference in steady state (CISS) images). Using the intranet, all images are imported into Leksell GammaPlan® (LGP) (Elekta AB), coregistered, and fused. Before treatment planning and radiation dosimetry, the anterior optic pathways and the optic tracts, pituitary gland, pituitary stalk up to the tuber cinereum, brainstem, and internal carotid arteries (ICA) are delineated.

Radiosurgical Target

At the beginning of our practice of pituitary radiosurgery for intractable pain, the entire pituitary gland was considered the main target. However, as we gained more experience, the center of the target was shifted to the junction between the pituitary gland and the pituitary stalk, with intentional inclusion of more than half of the pituitary gland and the lower part of the pituitary stalk in the 50% prescription isodose area [26, 29]. In particular, such a technique allows us to protect (at least in part) the adenohypophysis from high-dose irradiation. Similar targeting is generally used by other colleagues [21, 36, 37], unless ablation of the adenohypophysis for hormone suppression is the treatment goal [22]. In our practice, pituitary radiosurgery is usually performed with use of a single 8 mm isocenter; use of two or three isocenters for this purpose has been also reported [21, 22, 36].

Treatment Dose

In our experience, the maximal radiation dose delivered to the target at the 100% prescription isodose line has varied from 140 to 180 Gy and has been slightly lowered in patients with poststroke thalamic pain, considering their relatively long life expectancy and corresponding risk of delayed treatment-related morbidity. Nevertheless, at present, we think that maximal doses of 140 and 160 Gy are fully appropriate in cases of noncancer and cancer pain, respectively. Similar maximal doses for pituitary radiosurgery have been used by other colleagues [21, 25, 36, 37]. As an exception, Backlund et al. [22, 23] have applied 200–250 Gy to the target with the goal of pituitary gland ablation.

Protection of the Anterior Visual Pathways and Other Critical Structures

Protection of the anterior visual pathways is of paramount importance during high-dose irradiation of the pituitary gland. In our current practice, the maximal doses delivered to the anterior visual pathways are consistently kept below 10 Gy; previously, the dose limit was even lower (8 Gy). This can be attained with several maneuvers. First, the gamma angle may be reduced to 75–85°, which enables positioning of the isodose distribution line in parallel to the optic nerves and tracts. Second, beam plugging may be applied for modification of the safe dose distribution. Third, if the pituitary stalk is too short, the position of the applied isocenter may be lowered. In such cases, use of two 4 mm isocenters, or 8 and 4 mm isocenters, for radiation delivery may also facilitate safe treatment planning [21, 36]. Of note, the unaffected anterior optic pathways' tolerance of SRS may be a bit higher, and irradiation of their limited volume with a dose of up to 15 Gy may be free of any negative consequences, at least during short- and medium-term follow-up [25]. In addition, we limit the maximal dose delivered to the brainstem to 14 Gy and try to minimize the irradiation of cranial nerves within the cavernous sinuses and ICA to avoid their radiation injury. Before the start of radiosurgical treatment, the dose distribution area is confirmed on 3D reconstructed images within LGP with regard to all critical structures [26, 29, 31–35].

Clinical Results

Only six uncontrolled series involving small numbers of patients (from 7 to 27) and two case reports on clinical application of pituitary radiosurgery by means of the Gamma Knife for management of intractable pain have been published to date (Table 1). In addition, according to a personal communication from Dr. Chung Ping Yu (in 2020), pituitary radiosurgery for management of cancer pain has been continually applied at the Gamma Knife Center at Canossa Hospital (Hong Kong, SAR, China), demonstrating high clinical efficacy and safety.

In 1968–1972, Backlund et al. [22, 23] applied pituitary radiosurgery in eight postmenopausal women (age range 50–76 years) with advanced breast carcinoma and bone metastases. Most patients had a sufficiently long free interval between treatment of the primary cancer and appearance of the first metastatic lesion. Four patients died at 3 weeks and at 1, 3, and 8 months, respectively, after SRS; the others were followed up for between 4 and 9 months. In the latter subgroup, considerable pain relief and an increased sense of well-being were noted [22, 23].

In 1998, Liscák and Vladyka published a case report [25] highlighting the result of pituitary radiosurgery in a 57-year-old woman with bone metastases from a breast adenocarcinoma. Eight years before SRS, the patient had undergone surgery for primary cancer, but she was subsequently diagnosed with multiple liver and bone metastases, which were treated with chemotherapy. In particular, she suffered from severe cervicocranial pain due to a metastatic lesion in the C2 vertebra. Within 2 weeks after pituitary radiosurgery, symptomatic improvement and complete pain relief were noted, and they lasted for 24 months, at which time, her condition deteriorated significantly. The patient died 26 months after SRS [25].

A multicenter prospective protocol directed at evaluation of pituitary radiosurgery for management of cancer pain was

Table 1. Reported results of pituitary radiosurgery by means of the Gamma Knife for management of intractable pain syndromes

Study	Institution	Number of patients (years of treatment)	Cause of pain	Radiosurgical target	Maximal dose (Gy)	Short-term results	Length of follow-up (months)	Long-term results	Side effects and complications
Backlund et al. (1972) [22]	Sophiahemmet Hospital, Stockholm	8/4[a] (1968–1972)	Bone metastases of breast carcinoma	Anterior two thirds of the pituitary gland (adenohypophysis)	200–250	ND	4–9	The 4 evaluated patients obtained considerable pain relief and improved well-being	The intended decrease in pituitary hormone levels was not achieved. Diabetes insipidus occurred frequently
Liscák and Vladyka (1998) [25]	Na Homolce Hospital, Prague	1	Bone metastases of breast carcinoma	Pituitary gland	150	Complete pain relief within 2 weeks after SRS	26	Complete pain relief lasted for 24 months after SRS	Decreased serum cortisol level at long-term follow-up after SRS. Hormonal replacement therapy needed for hypocortisolism
Hayashi et al. (2002) [26]	Tokyo Women's Medical University, Tokyo; Na Homolce Hospital, Prague; Canossa Hospital, Hong Kong	9[b]	Bone metastases of different cancers	Junction between the pituitary gland and stalk	160	Complete pain relief in all patients within several days after SRS	1–24	In all patients, complete pain relief without use of analgesic medication was permanent	None
Hayashi et al. (2004) [33]	Tokyo Women's Medical University, Tokyo	10 (2002–2004)	Bone metastases of different cancers	Junction between the pituitary gland and stalk	160	Significant pain reductions in all patients within several days after SRS	1–6	Complete pain relief (with or without use of morphine) was attained in 8 patients and significant pain reductions in 2. In all patients, the analgesic effect after SRS was permanent	None
Kwon et al. (2004) [36]	Samsung Medical Center, Seoul	7 (2003–2004)	Metastasis of different cancers into various organs	Junction between the pituitary gland and stalk	150–160	Significant pain reductions in all patients within a few days (mean 4.1 days) after SRS	1–13	At the time of death or the last follow-up after SRS, pain relief was preserved in 5 patients (71%). Even in 2 patients with recurrent pain (at 1 and 6 months after treatment), it was less intense than before SRS. On average, a 19.1% reduction in analgesic doses was noted. Six patients (86%) were very satisfied with the results of the treatment	No new hormonal abnormalities, except in 1 patient with pre-existing hypopituitarism and diabetes insipidus

(continued)

Table 1. (continued)

Study	Institution	Number of patients (years of treatment)	Cause of pain	Radiosurgical target	Maximal dose (Gy)	Short-term results	Length of follow-up (months)	Long-term results	Side effects and complications
Hayashi et al. (2007) [29]	Tokyo Women's Medical University, Tokyo	27/24[a] (2002–2006)	Thalamic pain after hemorrhagic stroke (in 17 cases) or ischemic stroke (in 6 cases) and after successful SRS for thalamic lymphoma (in 1 case)	Junction between the pituitary gland and stalk	140–180	Pain reductions in 17 patients (71%), usually within 48 hours after SRS	12–48	Analgesic effects lasted <3 months in 5 patients and <6 months in another 5. At the time of the last follow-up, pain reductions were noted in 5 patients (21%). After treatment, 10 patients (42%) showed marked improvements in motor function as a result of pain reduction	During long-term follow-up, 10 patients (42%) experienced posttreatment side effects, which included hormonal changes (in 8 patients; 33%) within a median time interval of 6 months after SRS, and transient diabetes insipidus (in 2 patients; 8%) with transient hyponatremia (in 1 patient; 4%). One patient (4%) showed clinical deterioration due to aggravation of numbness despite a significant reduction in pain
Lovo et al. (2019) [37]	International Cancer Center, San Salvador	11/10[a] (2016–2018)	Metastasis of different cancers into various organs, including bones (in 7 cases), and peritoneal carcinomatosis or brachial plexus involvement (in 3 cases)	Neurohypophysis	150	Significant pain reductions in 8 patients within a few days (mean 2.8 days) after SRS. In all of them, reductions of at least 25% in analgesic doses were noted	1–12	Excellent results (i.e., minimal or absent pain) and good results (pain adequately controlled with medication) were noted by 2 and 6 patients, respectively, 1 month after SRS. In 6 of them, reductions of at least 25% in analgesic doses were noted. A long-lasting analgesic effect (for about 1 year) was observed in 1 patient. At the time of death, 3 patients had no pain, and in 2, it reappeared only at the end of life	No morbidity according to regular clinical assessments
Golanov et al. (2020) [21]	Burdenko Neurosurgical Institute, Moscow	1	Liver and lung metastases of pancreatic cancer	Junction between the pituitary gland and stalk	150	Significant pain reduction within 1 day after SRS	1	The maximal analgesic effect was reached on the fifth day after SRS and was permanent. Significant reductions in analgesic doses and prominent improvements in quality of life were noted	None

ND no data, *SRS* stereotactic radiosurgery
[a]Number of patients treated/number of patients analyzed
[b]This series partly overlaps with other reports

initiated in 2002 [26]. The eligibility criteria included metastatic bone disease as a cause of pain, a KPS score >40, ineffectiveness of previous pain management, good control of pain with morphine, and no cranial irradiation by means of SRS, FRT, or WBRT in the past. The study enrolled 9 patients, who were treated by our group at Tokyo Women's Medical University (2 cases), Canossa Hospital in Hong Kong (2 cases), and Na Homolce Hospital in Prague (5 cases). In all individuals, complete pain relief without medication was noted within a few days after pituitary radiosurgery. This treatment effect did not differ between hormone-dependent and other cancers, and it was consistently maintained for the rest of the patients' lives (range 1–24 months) [26].

From 2002 till 2004, our group performed pituitary radiosurgery in 10 patients (mean age 58.4 years) with bone metastases originating from breast cancer (in 2 cases), prostate cancer (in 2 cases), colon cancer (in 2 cases), esophageal cancer (in 2 cases), lung cancer (in 1 case), and cancer of unknown primary (in 1 case) [33]. Significant pain reduction was observed in all cases within several days after treatment. All patients were followed up after SRS until their deaths. Complete pain relief (with or without continuing use of morphine) was occasionally noted in 8 of them and significant pain reduction in 2. The treatment effects did not differ between hormone-dependent (breast and prostate) cancers and other cancers, and these effects persisted for the rest of the patients' lives (range 1–6 months) in all cases [33].

In 2003–2004, Kwon et al. [36] conducted a prospective evaluation of pituitary radiosurgery in 7 patients (mean age 53.9 years) with pain caused by metastases of different cancers (lung cancer, colon cancer, stomach cancer, and a high-grade meningioma) into various organs. The mean duration of symptoms before SRS was 9.9 months (range 2–42 months), and the effect of morphine therapy was not satisfactory. The patients' pain intensity before treatment corresponded to a Visual Analogue Scale (VAS) score of 8–10 out of 10. Significant pain reduction (>50%, quantified by use of the VAS) was noted in all patients within a few days (mean 4.1 days) after SRS. The length of posttreatment follow-up varied from 1 to 13 months (median 1.5 months). At the time of death (which occurred in 4 patients) or the last clinical evaluation, pain relief (with continuing use of opioid or nonopioid analgesics) was preserved in 5 patients (71%). On average, a reduction in analgesic doses by 19.1% was noted. In 2 cases, pain recurred (at 1 and 6 months), but it was less intense than before SRS. Six patients (86%) were very satisfied with the results of their treatment [36].

Between 2002 and 2006, we applied pituitary radiosurgery for management of thalamic pain in 27 patients, and 24 of them (mean age 64.7 years) were analyzed in detail [29]. Their symptoms developed after a thalamic hemorrhage (in 17 cases), thalamic infarction (in 6 cases), and effective SRS of a thalamic lymphoma, which was considered a radiation-induced stroke (in 1 case). The pain was resistant to various applied treatment modalities, and the mean duration between its onset and pituitary radiosurgery was 91.2 months. Initial pain reduction was noted in 17 of the 24 patients (71%), usually within 48 h after irradiation. However, this treatment effect lasted <3 months in 5 patients and <6 months in another 5. At the time of the last follow-up (mean 35 months, range 12–48 months), pain reduction was noted in 5 patients (21%). In addition, as a collateral result of pain reduction after pituitary radiosurgery, 10 patients (42%) showed marked improvements in their motor function. In no case was pituitary radiosurgery effective for management of preexisting numbness [29].

During 2016–2018, Lovo et al. [37] performed a prospective evaluation of pituitary radiosurgery in 11 terminally ill cancer patients with opioid-refractory pain caused by metastases into various organs, peritoneal carcinomatosis, or brachial plexus involvement. Of the total cohort, 10 patients (median age 64 years) were eligible for follow-up examinations. Seven of them had metastatic bone disease, and the others suffered from neuropathic or visceral pain, whose intensity before treatment corresponded to a VAS score of 7–10 out of 10. A significant pain reduction (≥50%, quantified by use of the VAS) within 2–5 days (mean 2.8 days) after SRS was noted in 8 patients. In the first week and at 1 month after SRS, 4 and 2 responders, respectively, categorized their treatment result as excellent (with minimal or absent pain) and 3 and 6 responders, respectively, classified their result as good (with pain adequately controlled with medication). At the same time points, reductions of at least 25% in analgesic doses were noted in 8 and 6 cases, respectively. After treatment, all patients were followed up for the rest of their lives (median 3.9 months, range 1–12 months). At the time of their deaths, 3 patients had no pain, and in 2, it appeared only at the end of life. A long-lasting analgesic effect (for around 1 year) was observed in 1 case. However, 2 patients, both with neuropathic and/or visceral pain, never responded to pituitary irradiation [37].

In the most recent case report, published in 2020, Golanov et al. [21] described their experience with pituitary radiosurgery in a 77-year-old woman with liver and lung metastases from a pancreatic ductal adenocarcinoma, presenting with visceral pain, which significantly impaired her quality of life (QOL). There was only a limited response to opioids (morphine and tramadol), whose administration was accompanied by side effects. A significant pain reduction was noted 1 day after SRS; the maximal analgesic effect was reached on the fifth posttreatment day and lasted until the patient's death 1 month later. This allowed a reduction in the administered analgesic doses and was accompanied by a permanent and marked improvement in QOL [21].

According to the aforementioned publications, at least temporary pain relief after pituitary radiosurgery was noted in 57 of the 66 evaluated cases (86%). The analgesic effects of treatment were most frequent and durable in the presence of metastatic bone disease but were not limited to that pathological condition or to cases of hormone-dependent cancers.

Side Effects and Complications

Pituitary radiosurgery has not been accompanied by any early side effects or complications in our experience or in other studies.

None of our 10 patients treated for cancer pain demonstrated hypopituitarism after high-dose irradiation of the pituitary gland and stalk. Even among 24 patients who were treated for nonmalignant thalamic pain and were followed up for at least 12 months after pituitary radiosurgery, hormonal changes were noted only in 8 (33%) and the median time interval from SRS to their development was 6 months (mean 9 months) [29]. In all of those cases, decreases in triiodothyronine (T3) and thyroxine (T4) levels with a normal thyroid-stimulating hormone (TSH) level (in 7 patients) or a diminished TSH level (in 1 patient) were demonstrated. This was an isolated abnormality in 5 patients, whereas 3 others had an additional decrease in their gonadotropin level, and one of them also demonstrated hyperprolactinemia and growth hormone (GH) deficiency. Hormonal replacement therapy for hypothyroidism was required in 3 patients [29]. The patient reported by Liscák and Vladyka [25] showed decreased serum cortisol levels during long-term follow-up after pituitary radiosurgery, which necessitated hormonal replacement therapy with hydrocortisone. Finally, Kwon et al. [36] noted aggravation of pre-existing hypopituitarism within 1 month after SRS in 1 of 7 patients (14%) in their series.

Overall, 2 of 34 patients (6%) treated with pituitary radiosurgery by our group and followed up thereafter showed transient diabetes insipidus at 6 months after treatment, and in one of them, it was accompanied by transient hyponatremia. Both of these patients were treated for poststroke thalamic pain [29]. Backlund et al. [22, 23] also frequently noted posttreatment diabetes insipidus in their patients. Kwon et al. [36] marked aggravation of pre-existing diabetes insipidus within 1 month after SRS in 1 of 7 patients (14%) in their series.

Visual deterioration was not observed in any patient in our cohort or in the other reported series.

Finally, one patient who was treated for poststroke thalamic pain and experienced a significant reduction in pain after pituitary radiosurgery suffered from a prominent aggravation of numbness, which negatively affected his QOL [29]. This was the only case of a neurological complication in our experience.

Overall, although the possibility of treatment-related side effects and complications after pituitary radiosurgery should be taken into consideration, their rates and clinical significance are clearly much lower than the historically reported rates of postoperative morbidity after surgical or chemical hypophysectomy [22, 28].

Histopathological Changes After Pituitary Radiosurgery

There is limited information on histopathological changes in the targeted structures after pituitary radiosurgery.

In the series reported by Backlund et al. [22], an autopsy was done in 3 patients who died 1–8 months after treatment. The demonstrated findings were rather uniform. Serial sectioning of the pituitary gland showed a very distinct radiation-induced lesion in the targeted adenohypophysis, which was mostly confined to the 70–80% isodose areas (i.e., to an irradiation dose of 185 ± 15 Gy). This area was surrounded by normal glandular tissue. In one additional patient who died 3 weeks after irradiation, no macroscopic lesion was noted, but pyknosis and other nuclear changes were scattered throughout the adenohypophysis. A detailed histopathological examination of the targeted tissue was performed in only one case and revealed an intact fibrillar stroma and occasional hemorrhages within the radiation-induced lesion, along with congested vessels at its edge. Within the adjacent preserved glandular tissue, a few cells were degenerated with pyknotic nuclei, whereas in the outer peripheral area, the tissue was fibrotic and its parenchyma was reduced. A slight inflammatory reaction in the surviving glandular tissue was noted without signs suggesting regeneration of the parenchyma. No microscopic changes were observed in the vicinity of the target; the bone of the sella, the optic pathways, and the hypothalamus appeared completely normal [22].

Utsuki et al. [46] reported a case of a 62-year-old patient who underwent pituitary radiosurgery (maximal dose 180 Gy) at Tokyo Women's Medical University for thalamic pain, which developed after effective SRS for a thalamic lymphoma. The treatment resulted in complete pain relief, which allowed a decrease in opioid doses, but the patient died 6 months later because of a tumor recurrence. An autopsy revealed massive radiation-induced necrosis of the pituitary gland in the vicinity of its junction with the pituitary stalk, but the latter was mostly unaffected. Also, approximately half of the adenohypophysis was preserved. There were no changes in the anterior optic pathways or the hypothalamus [46].

Remaining Questions and Future Research Perspectives

Since all studies on pituitary radiosurgery reported to date have been based on evaluation of limited numbers of enrolled patients who were not directly compared with any control group and frequently did not undergo systematic and objective follow-up assessments, the efficacy and safety of this treatment modality for management of intractable pain, the factors associated with favorable outcomes, the mechanisms of therapeutic effectiveness, and the dynamic imaging and histopathological changes in the pituitary gland and stalk definitely require additional investigations. To clarify some of these issues, an open-label multicenter prospective randomized controlled trial (clinicaltrials.gov identifier NCT02637479) was initiated at the end of 2015 in France [47]. Patients in palliative care who have multiple bone metastases, suffer from opioid-refractory nociceptive or mixed cancer pain, and demonstrate a KPS score >40 are considered eligible for enrollment. The experimental group is receiving pituitary radiosurgery by means of the Leksell Gamma Knife (with 160 Gy being delivered to the pituitary gland) along with the standard of care for pain management according to the existing guidelines, whereas the randomly assigned control group is being treated with the standard of care for pain management alone. Longitudinal clinical evaluations are scheduled at ten predefined time points from the baseline up until the sixth posttreatment month. The primary endpoint is the analgesic efficacy of pituitary radiosurgery, assessed on the fourth posttreatment day, and the investigators expect to achieve a clinical improvement (represented by a Numeric Pain Intensity Scale score of <4 out of 10) in 70–90% of cases. The secondary objectives include evaluation of treatment safety—in particular, ophthalmological and endocrine tolerance, neurological symptoms, pain recurrence, analgesic drug consumption, QOL, and patient satisfaction. In addition, the mechanisms of the analgesic effects of pituitary radiosurgery will be analyzed on the basis of a comparison of metabolic consumption and connectivity by means of ^{18}F-fluorodeoxyglucose positron emission tomography (PET) performed before and on the fourth day after irradiation. Structural changes in the pituitary gland will be assessed by postcontrast MRI 3 months after treatment [47]. Currently, this trial is ongoing and recruiting patients, and its results are eagerly anticipated.

There is a possibility that the analgesic effects of pituitary radiosurgery are more pronounced in cases of metastasized hormone-dependent cancers (e.g., breast and prostate carcinomas); thus, it may be preferable to consider tumor histology during data analysis and/or selection of more homogeneous patient cohorts for clinical studies. Moreover, it may also be possible to re-examine whether associated suppression of pituitary hormone secretion impacts the growth potential and dissemination of such neoplasms, as has been extensively discussed in the past [2, 4, 14–16, 21, 48]. Since the efficacy of hypophysectomy may be more pronounced in patients who have a longer time interval between treatment of their primary cancer and development of distant metastases [2], have tumors that have initially responded to endocrine therapy [2], and experience positive effects after administration of opioid analgesics [21, 26, 29, 31–36], it may be reasonable to evaluate whether these factors can be used for selection of appropriate candidates for such treatment.

Of particular interest may be a comparison of pituitary radiosurgery with alternative SRS targets that may be used for management of intractable pain—for example, radiosurgical cingulotomy, mesencephalotomy, or thalamotomy [24, 44, 45]. This issue was in part addressed in the systematic review done by Roberts and Pouratian [28], who analyzed six related studies involving 113 patients with consideration of the SRS target (the pituitary versus the thalamus) and pain etiology (cancer versus noncancer pain). The rate of significant pain relief within hours or days after irradiation was at least 56% (and could have been as high as 73%). However, after the initial treatment effect, a recurrence of pain was noted in 60% of patients (and in 32% of patients after pituitary radiosurgery, all of whom had noncancer pain), and the rate of significant pain relief at the time of the last follow-up or death had dropped to 35%. In total, at least 33% of patients with cancer pain demonstrated durable symptomatic improvements, and in this subgroup, the efficacy of pituitary radiosurgery was found to be superior, with an 87% success rate. On the other hand, 39% of patients with noncancer pain showed durable relief, and in those individuals, radiosurgical thalamotomy was considered more effective, with a 65% success rate. Adverse radiation effects were noted in at least 23% of cases (occurring in 40% after pituitary radiosurgery and in 9% after radiosurgical thalamotomy) and were mainly related to hormonal deficits [28]. Of similar importance may be a comparative evaluation of the clinical efficacy and safety of pituitary radiosurgery versus nondestructive and destructive neurosurgical procedures used for management of intractable pain [27, 40, 43], and such clinical studies are definitely warranted.

It may also be worth reconsidering whether modern pituitary radiosurgery, characterized by high precision and a good safety profile, could play any role in altering the clinical course of progressive diabetic retinopathy, which historically was regarded as a potential indication for surgical and nonsurgical hypophysectomy [16, 49–51], although such treatment has been fully abandoned over time.

Effects of High-Dose Irradiation on the Hypothalamic–Pituitary Axis

The mechanisms of the analgesic effects of pituitary radiosurgery should be investigated in detail as well, and for this purpose, systematic longitudinal evaluations with functional and metabolic neuroimaging may effectively provide novel insights. For example, in our series of patients with metastatic bone disease, a proton magnetic resonance spectroscopy (^{1}H-MRS) study demonstrated significant increases in local N-acetylaspartate levels within 24 h after high-dose irradiation of the pituitary gland and stalk, indicating that this treatment may result in modulation of hypothalamic and thalamic neuronal network activity [26]. Possible involvement of the nociceptin/orphanin FQ–nociceptin peptide (N/OFQ-NOP) receptor system in realization of the analgesic effects of pituitary radiosurgery is another appealing topic for future research work [21].

One of the most intriguing facts about pituitary radiosurgery is that according to the existing data, the risk of endocrine abnormalities after high-dose irradiation of the intact pituitary gland and stalk is comparable to that after SRS of sellar tumors with use of much lower doses. This can be explained in several ways [29]. First, the effect of irradiation on the hypothalamic–pituitary axis not only may depend on the dose and target volume but also may be associated with the age of the patient (both younger and older individuals have been declared to be more susceptible) and with prior compromise of local neuronal integrity by the presence of a mass lesion or a previous surgical procedure [52, 53]. Of note, in the experience reported by Backlund et al. [22, 23], the desired suppression of pituitary hormone secretion was not achieved despite irradiation of the intact adenohypophysis with a dose of 200–250 Gy (making the authors very disappointed that this treatment objective was not achieved!); thus, the currently employed radiation doses of 140–160 Gy may simply be insufficient to cause ablation of a normal pituitary gland. On the other hand, as the experience of Kwon et al. [36] demonstrated, patients with pre-existing hypopituitarism may be at higher risk of its aggravation after pituitary radiosurgery. Second, a sharp falloff in the radiation dose outside the target area may result in preservation of adjacent normal glandular tissue [22, 46], and this may be sufficient for hormonal secretion. Third, there is evidence that the primary site of radiation-induced damage of the hypothalamic–pituitary axis is not the pituitary gland itself but the hypothalamus and the pituitary stalk, which are more radiosensitive structures whose dysfunction can significantly influence the progression of posttreatment hypopituitarism [52–54]. However, this cannot completely explain the issue with pituitary radiosurgery: while careful treatment planning in such cases enables hypothalamic injury to be avoided (thereby reducing the risk of associated complications), inclusion of the lower pituitary stalk in the high-dose irradiation area is currently considered an important prerequisite for treatment success. Fourth, the risk of hypopituitarism after SRS or FRT in the vicinity of the hypothalamic–pituitary axis is clearly time dependent; thus, patients who have undergone pituitary radiosurgery, particularly those with cancer pain, may simply have too short a life expectancy to demonstrate endocrine abnormalities [29]. Meanwhile, it is somewhat surprising that in our series, hypothyroidism was the most common endocrinological abnormality after pituitary radiosurgery, since the hypothalamic–pituitary–thyroid axis is usually considered relatively resistant to radiation damage [53, 54]. In any case, additional studies on the dynamics of hormonal changes after high-dose irradiation of the pituitary gland and stalk and their possible interplay with the analgesic effects of this procedure are clearly needed.

Another striking finding is the discrepancy between the absence of structural changes in the pituitary gland and stalk on serial MRI after pituitary radiosurgery [26, 29, 31–35, 46] and histopathological identification of posttreatment necrosis in a few cases where an autopsy was done [22, 46]. More systematic studies employing advanced imaging modalities and volumetric evaluations of the targeted anatomical structures should be performed to clarify the time course of radiation-induced lesions.

Finally, comparison of the various available SRS modalities that can be used for pituitary radiosurgery in patients with intractable pain, with regard to both clinical effectiveness and complication profiles, may be of practical interest. In fact, such treatment can be readily accomplished utilizing a linear accelerator (LINAC), CyberKnife (Accuray; Sunnyvale, CA, USA), or other radiosurgical devices. Our group is currently evaluating possible application of heavy particle (carbon ion) irradiation of the pituitary gland, since it may tremendously increase the amount of radiation energy delivered to the target. Whether this or some other radiological and radiobiological parameters (e.g., the dose rate or the biologically effective dose) may increase the efficacy of pituitary radiosurgery—in particular, the durability of its analgesic effects—and how it may impact the risks of related adverse reactions and complications should be investigated in the future.

Conclusion

Pituitary radiosurgery has demonstrated highly promising results in management of intractable pain syndromes caused by disseminated cancer (in particular, metastatic bone disease) and thalamic stroke. According to the available data, the analgesic effects of this procedure are comparable with those of both surgical and chemical hypophysectomy, but

only a few associated side effects and complications are observed during both short- and medium-term follow-up. However, the low-quality studies reported to date provide only level IV evidence of the efficacy of such treatment and do not support any meaningful clinical recommendations. Therefore, additional well-elaborated evaluation of this SRS technique, preferably performed in a multi-institutional and prospective fashion, is absolutely necessary. Similarly important are elucidation of the analgesic effects of hypophysectomy and understanding of their detailed mechanisms, particularly with regard to high-dose irradiation of the pituitary gland and stalk. Hopefully, additional clinical and basic investigations will bolster further developments in pituitary radiosurgery and expand its clinical role.

Acknowledgements The authors are thankful to Drs. Roman Liscák (from Na Homolce Hospital, Prague, Czech Republic), Emil Isagulyan, and Elizaveta Makashova (both from Burdenko Neurosurgical Institute, Moscow, Russia) for sharing their experiences with pituitary radiosurgery in patients with cancer pain.

Conflict of Interest The authors have no conflict of interest concerning the reported materials or methods.

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Feasibility and Significance of Dose Adaptation via Linear Couch Translations to Correct for Rotational Shifts During Frameless Brain Radiosurgery with the Gamma Knife Icon™

Joey P. Cheung, Olivier Morin, Steve E. Braunstein, Penny K. Sneed, Philip V. Theodosopoulos, Michael W. McDermott, and Lijun Ma

Abstract *Objective:* The present study aimed to examine the technical feasibility and effectiveness of adapting the radiation dose distributions with three-dimensional (3D) linear couch translations in contrast to full six-dimensional couch maneuvers to correct for rotational shifts during frameless radiosurgical treatment with the Gamma Knife Icon™ (Elekta AB; Stockholm, Sweden).

Methods: The original magnetic resonance images used for radiosurgery treatment planning (15 targets) were digitally processed to simulate rotational shifts of ±1, ±2, ±3, ±5, and ±10 degrees in the transverse plane and imported back into Leksell GammaPlan® (Elekta AB), creating "uncorrected" treatment plans. In addition, geometrically optimized 3D translation shifts were consequently applied to each isocenter in all "uncorrected" treatment plans to account for systematically introduced rotational shifts and to produce "corrected" treatment plans. The differences in the dose distribution between the original treatment plans and the "uncorrected" and "corrected" treatment plans were calculated and compared at each rotational shift position.

Results: The "uncorrected" treatment plans resulted in a significant deterioration in target coverage (by 8–72%) and selectivity (by 2–42%), with some targets being missed completely with rotations of ±3 or more degrees. In contrast, in all "corrected" treatment plans, the average decreases in target coverage and selectivity were only 1% (maximum values 4–5%).

Conclusion: Applications of 3D linear couch translations successfully overcome gross uncertainties in dose distributions caused by up to ±10 degrees of rotational shifts in a target. As a result, rapid dose adaptation with 3D couch translations is unique and effective for frameless radiosurgery with the Gamma Knife Icon™.

Keywords Cone beam CT · Dose adaptation · Frameless radiosurgery · Gamma Knife Icon™ · Gamma Knife radiosurgery · Rotational shift · Stereotactic radiosurgery Treatment accuracy

Introduction

Modern technological devices for Gamma Knife surgery (GKS) possess high levels of precision for radiation delivery to both small and large intracranial targets during treatment with utilization of a frame-based or frameless patient positioning system (PPS) [1]. This is mostly achieved by the use of a large number of irradiation beams (192–201 fixed cobalt 60 (^{60}Co) sources) and their conical geometry. According to the manufacturer (Elekta AB; Stockholm, Sweden), the mechanical accuracy of the current PPS in Gamma Knife Perfexion™ is less than 0.35 mm, and this has been confirmed by several independent studies [2–5].

There has recently been growing interest in multisession GKS, which can be performed either as volume-staged treatment (if the lesion is too large for delivery of a sufficient therapeutic dose in a single session) or as hypofractionated treatment (which may be suitable for targets in the vicinity of critical brain structures in order to reduce toxicity). The technical possibility, clinical feasibility, and practicality of such radiosurgical strategies have been demonstrated [6–8]. For multisession GKS with the Gamma Knife Perfexion™, the head of the patient may be immobilized with a vacuum-assisted bite block relocatable system named Gamma Knife Extend™ (Elekta AB). Many groups have verified the submillimeter precision of this device [6–8], but its use requires well-functioning dentures, sufficient cooperation, and good

J. P. Cheung · O. Morin · S. E. Braunstein
P. K. Sneed · L. Ma (✉)
Department of Radiation Oncology, University of California San Francisco (UCSF), San Francisco, CA, USA
e-mail: lijun.ma@ucsf.edu

P. V. Theodosopoulos · M. W. McDermott
Department of Neurosurgery, University of California San Francisco (UCSF), San Francisco, CA, USA

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*,
Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_16,

performance status of the patient in order to tolerate the treatment session, which typically lasts 10–30 min.

In contrast, the latest Gamma Knife model, named Gamma Knife Icon™ (Elekta AB), allows delivery of frameless GKS with thermoplastic mask–based head immobilization. This radiosurgical device is equipped with integrated cone-beam computed tomography (CT) and an infrared camera system for real-time motion tracking. For correction of rotational shifts from the original simulation scan, online adaptive replanning is applied. Thus, any positional deviations of the target from the initial treatment setups are subsequently compensated for, and this is achieved with couch motions. However, the current type of couch for the Gamma Knife Icon™ can perform three-dimensional (3D) translations only along the *x*, *y*, and *z* axes, and, as a result, residual uncertainties may be expected. Therefore, the question remains as to whether direct couch translations can effectively compensate for sizable rotational shifts during actual clinical treatments.

The objective of the present study was independent examination of the technical feasibility of adapting radiation dose distributions with 3D couch translations during treatment with the Gamma Knife Icon™, and quantification of its effectiveness for correction of rotational shifts and achievement of the dosimetric objectives of the original radiosurgical treatment plan.

Materials and Methods

This study was based on the evaluation of radiation dosimetry in seven patients treated with GKS for single or multiple intracranial tumors of various sizes ranging from 0.01 to 12.0 cc (Table 1). The distance from the lesion to the center of the magnetic resonance image varied from 2.4 to 7.5 cm; thus, the tested cohort was sufficiently representative of the locations of intracranial targets during realistic GKS (considering the 16.7 cm average width of the neurocranium in adult humans [9]). The original treatment planning was done by an experienced Gamma Knife user in accordance with the current standards of such treatment—in particular, with regard to target coverage and selectivity.

Image Processing

The original magnetic resonance images used for radiosurgery treatment planning were processed using a script in MATLAB (MathWorks; Natick, MA, USA) to rotate the imaged patient's skull within a stereotactic frame (Leksell G frame; Elekta AB) around the center of the image, thereby simulating rotational shifts (relative to the stereotactic coordinates) of ±1, ±2, ±3, ±5, and ±10 degrees within the transverse plane from the nominal position. Thereafter, the images were imported back into Leksell GammaPlan® (LGP) (version 10.2; Elekta AB), and the dose distribution was recalculated for each rotational shift position, creating "uncorrected" treatment plans.

Table 1 Intracranial target characteristics in the study cohort

Case number	Diagnosis	Target number	Target volume (cc)	Prescription dose (Gy)
1	Single brain metastasis	1	3.80	18.0
2	Vestibular schwannoma	1	4.64	12.5
3	Multiple meningiomas	1	12.00	15.0
		2	1.76	15.0
4	Pituitary adenoma	1	0.82	16.0
5	Multiple brain metastases	1	0.02	19.0
		2	0.04	19.0
		3	0.02	19.0
		4	0.02	19.0
		5	0.05	19.0
		6	0.02	19.0
6	Glioblastoma	1	10.84	16.0
7	Multiple brain metastases	1	1.05	18.5
		2	0.09	19.0
		3	0.01	16.5

Corrected Translation of Isocenters

To determine the corrections needed for translation of each isocenter on the rotation transformation matrix at each rotational shift position, a singular value decomposition (SVD)–based algorithm was applied to define the spatial transformation matrices (Fig. 1). Its application minimized the quadrature summed distance between multiple identical landmark points ($n \geq 4$) corresponding to the projection of the N-shaped bars of the stereotactic localizer, where the landmarks were identified and manually selected on the original and rotationally transformed magnetic resonance images. A similar method for planning multisession volume-staged GKS has previously been reported by our group [10]. Geometrically optimized 3D translation shifts based on the SVD-based algorithm were consequently applied to each isocenter in each "uncorrected" treatment plan, and the resulting isocenters were imported into LGP using a research script provided by the manufacturer to produce "corrected"

$$R_x(\theta) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos\theta & -\sin\theta \\ 0 & \sin\theta & \cos\theta \end{bmatrix}$$

$$R_y(\theta) = \begin{bmatrix} \cos\theta & 0 & \sin\theta \\ 0 & 1 & 0 \\ -\sin\theta & 0 & \cos\theta \end{bmatrix}$$

$$R_z(\theta) = \begin{bmatrix} \cos\theta & -\sin\theta & 0 \\ \sin\theta & \cos\theta & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

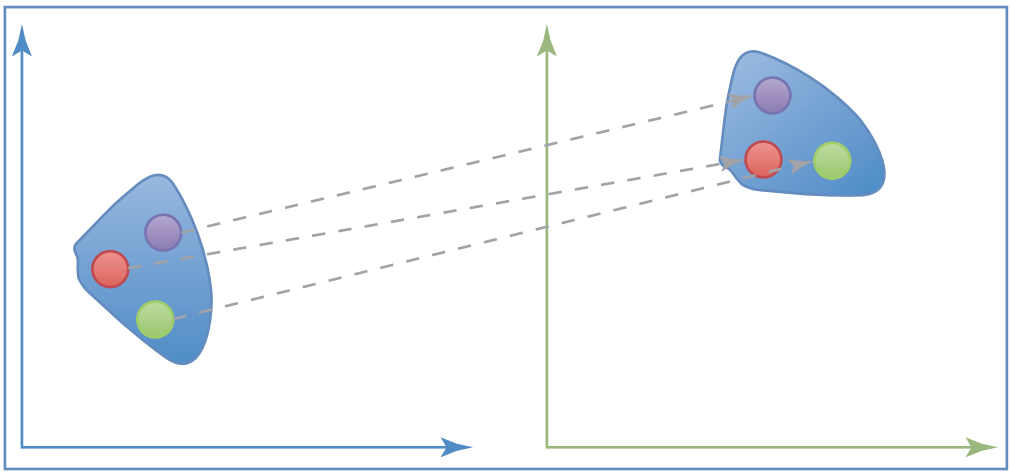

Fig. 1 Application of the singular value decomposition (SVD)–based algorithm for translation of the radiosurgical isocenters via the illustrated rotation transformation matrices to compensate for rotational shift errors

treatment plans and recalculation of the dose distribution for each rotational shift position.

Data Analysis

The differences in target coverage (the proportion of the target volume covered by the prescription isodose volume) and target selectivity (the proportion of the prescription isodose volume within the target volume) between the original treatment plan and the "uncorrected" and "corrected" treatment plans at each rotational shift position were calculated.

Results

The differences in target coverage and selectivity between the original treatment plan and the "uncorrected" and "corrected" treatment plans at each rotational shift position (from −10 to +10 degrees) in all evaluated cases are summarized in Fig. 2.

The "uncorrected" treatment plans resulted in average decreases in target coverage by 8%, 28%, 43%, 57%, and 72% with ±1, ±2, ±3, ±5, and ±10 degrees of rotation, respectively. With rotations of ±3 or more degrees, some targets were missed completely (a difference in target coverage of −1 (−100%)). The average decreases in target selectivity with application of the "uncorrected" treatment plans were 2%, 13%, 22%, 31%, and 42% with ±1, ±2, ±3, ±5, and ±10 degrees of rotation, respectively.

In contrast, with application of the "corrected" treatment plans, the average and maximum decreases in target coverage were only 1% and 4%, respectively, even with rotations of ±10 degrees. The differences in target selectivity were also dramatically improved and demonstrated an average −1% deviation in all evaluated cases, with values ranging from a −5% to +13%.

Illustrative Case

An example of dose distribution in a case of vestibular schwannoma with "uncorrected" and "corrected" treatment plans after a 10-degree rotational shift is shown in Fig. 3. The "corrected" treatment plan created with translation of isocenters according to the applied SVD-based algorithm to compensate for target rotation allowed sufficiently acceptable target coverage and selectivity.

In addition, the mean dose delivered to the adjacent cochlea was calculated (Fig. 4). With application of the "uncorrected" treatment plan, the mean dose increased in parallel with a greater degree of rotational shift, which moved the cochlea into the original position of the target, and decreased with rotation in the opposite direction (i.e., away from the original position of the target). In contrast, with application of the "corrected" treatment plan, the mean cochlea dose was nearly constant with 1% or less variation. Specifically, with use of the "uncorrected" treatment plan, a −1, −2, −3, −5, and −10 degrees of rotational shift, which moved the cochlea into the original position of the target, respectively resulted in a, roughly, 2, 4, 5, 8, and 7.5 Gy increase in its mean dose. With use of the "corrected" treatment plan, the maximum increase in the mean cochlea dose was only 0.7 Gy with a 5-degree rotational shift in both directions.

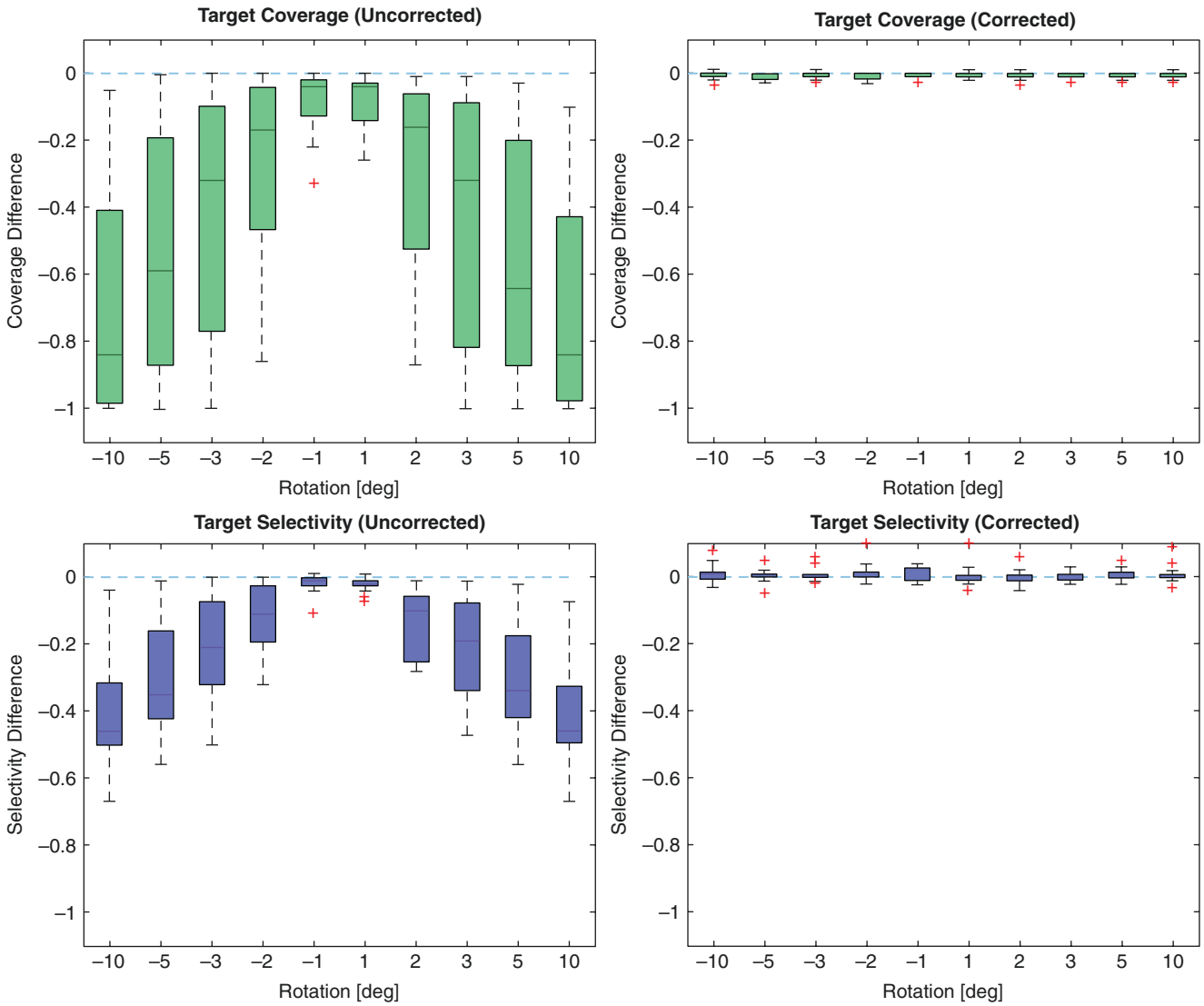

Fig. 2 Differences in target coverage and selectivity between the original treatment plan and the "uncorrected" and "corrected" treatment plans at each simulated rotational shift position (from −10 to +10 degrees) in all evaluated cases

Discussion

The presence of rotational shifts during radiosurgical procedures is well recognized. For example, in a study by Guckenberger et al. [11] the average and maximum shift values were 1.7 and 4 degrees, respectively, and the importance of their correction after the pretreatment setup and imaging were emphasized [11, 12]. From a geometrical standpoint, the smaller the size of the lesion and the longer the distance from the target location to the center of rotation, the larger the expected error in dose delivery if the treatment plan is left uncorrected [12].

While the overall number of cases in this proof-of-concept study was limited, the tested targets well represented the clinical range of various GKS-treated pathologies, their intracranial locations, and their sizes. The Gamma Knife Icon™ possesses 192 ^{60}Co sources, whose beams simultaneously irradiate the target from 180 degrees in azimuth angles surrounding the skull. Such a conical beam configuration not only facilitates their effective cross-firing, providing a steep dose falloff, but also makes the dose distribution robust to large rotational uncertainties. Since any rotational shift is physically equivalent to varying the depths of individual beams, leading to small variations in the tissue maximum ratios (TMR) as a whole, any decrease in the TMR value from one direction is largely compensated for by its increase from another direction, because of the general symmetry of the skull.

With use of the Gamma Knife Icon™, determination of any rotational shifts and their correction is achieved by

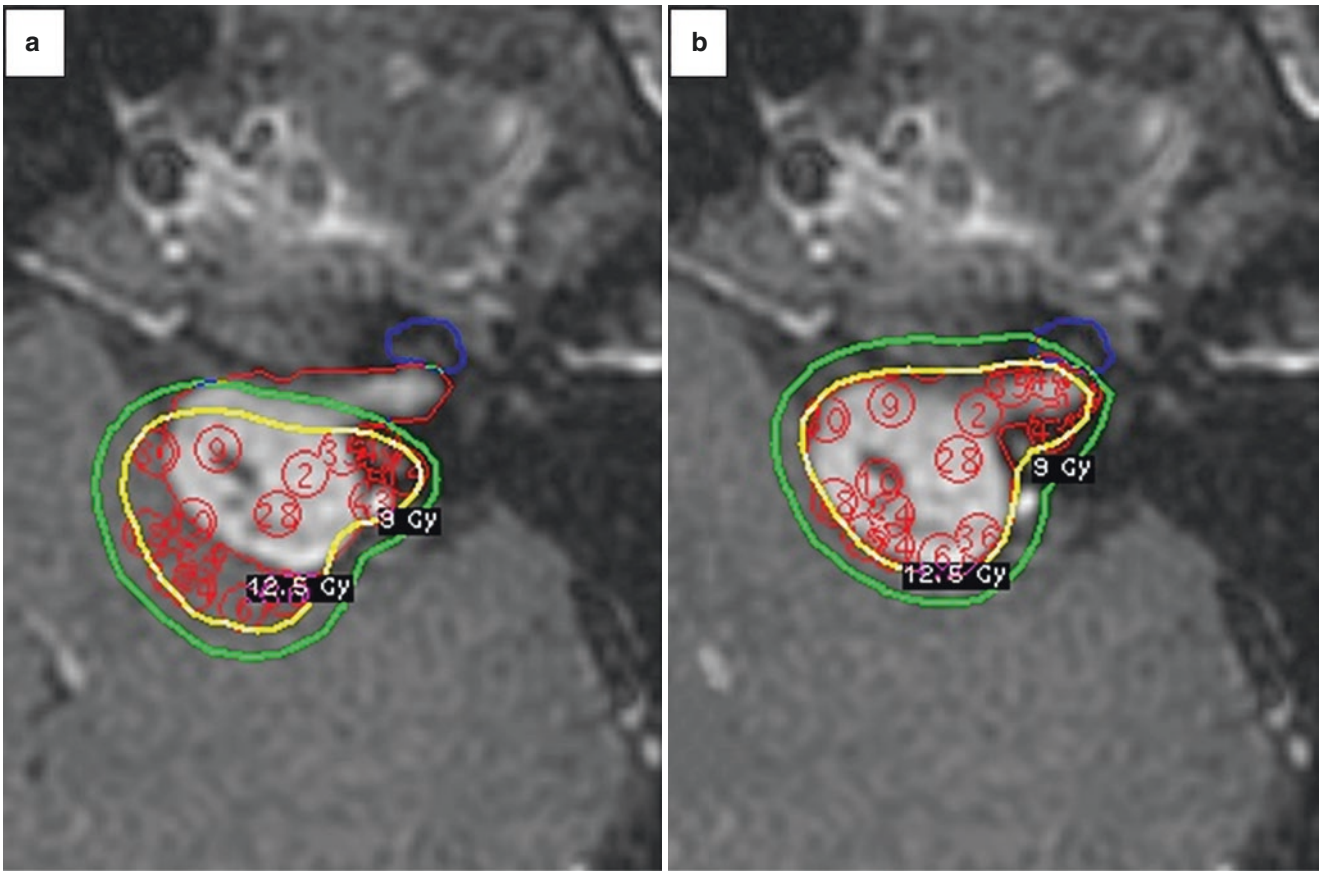

Fig. 3 Dose distribution during Gamma Knife radiosurgery for a vestibular schwannoma after simulation of a 10-degree rotational shift with application of "uncorrected" (**a**) and "corrected" (**b**) treatment plans. The latter provides sufficiently acceptable target coverage and selectivity. The adjacent cochlea is delineated in *blue*

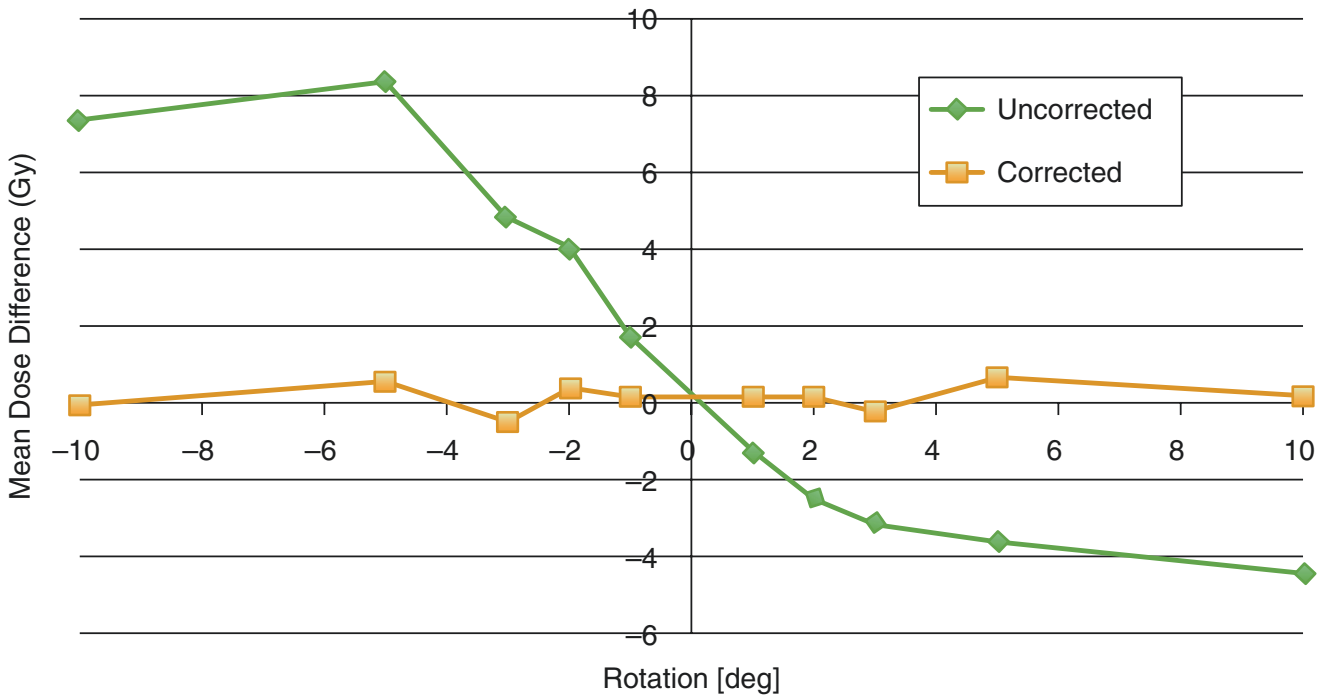

Fig. 4 Changes in the mean cochlea dose during Gamma Knife radiosurgery for a vestibular schwannoma with simulation of the rotational shifts of the target. Whereas application of the "uncorrected" treatment plan results in an increase in the mean dose delivered to the cochlea, with a greater degree of rotation moving the structure into the original position of the target, the mean cochlea dose is mostly stable with use of the "corrected" treatment plan

means of online adaptive replanning based on direct image registration techniques. In the present study, the evaluations of dose distributions presumed that with this radiosurgical device, target rotations could be corrected only with 3D couch translations, taking into account all the considered factors in the attenuation differences in the external patient anatomy during rotations. The results presented herein demonstrate that 3D translations of the isocenters from the original treatment plan for GKS to compensate for rotational shifts of the target provide sufficiently acceptable preservation of dose distributions in comparison with the original treatment plan. For all "corrected" treatment plans, the average decreases in target coverage and selectivity were only 1%, although they reached maximum values of 4–5% in certain cases.

The consistency of the results obtained with the "corrected" treatment plans also suggests that 3D couch translation is a technically feasible and clinically effective approach to preserve the dose distributions of the original treatment plan during treatment with the Gamma Knife Icon™, and mimics a virtual 6D couch. However, it is important to note that the present study did not test the consistency of mask-based immobilization or the infrared tracking capabilities of the radiosurgical device. A full assessment of the radiation dose delivery system is essential to determine the overall end-to-end accuracy—in particular, with regard to residual inconsistencies caused by rotational shifts that may occur during image-guided stereotactic irradiation.

Conclusion

Our independent examination demonstrated that during frameless GKS with the Gamma Knife Icon™, omission of corrections for rotational shifts may result in a significant compromise of dose distributions, even causing some small targets to be missed completely. On the other hand, application of 3D couch translations successfully overcomes gross uncertainties caused by up to ±10-degree rotational shifts. Nevertheless, even with application of such a technique, residual discrepancies (typically within 4–5% range) in target coverage and selectivity are occasionally noted. Replanning is therefore needed for such cases, which emphasizes the importance of careful patient setups, as well as monitoring and pretreatment evaluation of radiosurgical planning quality on a case-by-case basis, as is currently implemented in clinical workflow with the Gamma Knife Icon™.

Conflict of Interest Dr. Ma has a patent on radiosurgical technology from the Regents of the University of California and has previously received an educational honorarium and travel support from Elekta AB. The other authors have no conflict of interest concerning the reported materials or methods.

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Impact of the Skull Size on the Normal Brain Radiation Dose During Gamma Knife Radiosurgery: Results of a Pilot Study

Lijun Ma, Shannon Fogh, Steve E. Braunstein, Kurtis Auguste, Philip V. Theodosopoulos, Michael W. McDermott, and Penny K. Sneed

Abstract *Objective:* The objective of the present study was evaluation of the interrelationships between changes in the skull size and variations in the normal brain radiation dose during Gamma Knife surgery (GKS).

Methods: With use of systematic modeling within Leksell GammaPlan® (Elekta AB; Stockholm, Sweden) in each of 15 analyzed cases, the skull was "expanded" and "contracted" by variation of its measurement values from 0 to ±3 cm. The mean normal brain radiation dose was then computed for each variant of the adjusted skull size and compared with the original treatment plan. Variations in the maximum point dose delivered to selected critical anatomical structures were also investigated.

Results: With changes in the skull radius within ±3 cm, the maximum absolute deviation in the mean normal brain radiation dose was 0.8%. As the skull radius increased, the mean normal brain radiation dose also increased linearly (confidence level >99%) with a positive slope of 0.2% per centimeter of radius length change. The maximum point dose deviations in all evaluated critical anatomical structures did not exceed 0.5%, with an overall trend toward a dose increase in parallel with an increase in the skull radius.

Conclusion: The small skull size of pediatric patients may be associated with dosimetric advantages in terms of normal brain sparing during GKS.

Keywords Gamma Knife radiosurgery · Normal brain radiation dose · Pediatric radiosurgery · Radiation dosimetry Skull size

L. Ma (✉) · S. Fogh · S. E. Braunstein · P. K. Sneed
Department of Radiation Oncology, University of California San Francisco (UCSF), San Francisco, CA, USA
e-mail: lijun.ma@ucsf.edu

K. Auguste · P. V. Theodosopoulos · M. W. McDermott
Department of Neurosurgery, University of California San Francisco (UCSF), San Francisco, CA, USA

Introduction

Gamma Knife surgery (GKS) is a widely accepted treatment option for a variety of intracranial pathologies: benign and malignant tumors, arteriovenous malformations (AVM), epilepsy and other functional brain disorders, etc. [1–3]. The hallmark of GKS is a steep radiation dose falloff resulting in maximum sparing of the adjacent normal tissues, which allows prescription of high doses at the periphery of the target [4]. For example, for management of mesial temporal lobe epilepsy, a dose of 24–25 Gy is delivered at the 50% isodose line to cover the target volume of 7–8 cc [5], whereas to achieve a high probability of AVM obliteration, the marginal radiation dose should be ≥18 Gy [6]. Nevertheless, there is a major concern that high-dose GKS may result in increased toxicity and late neurocognitive sequelae associated with inadvertent irradiation of normal brain tissue. This may be particularly important during the treatment of children. Thus, the question has arisen as to whether the small skull size of pediatric patients would introduce any negative effect on normal brain sparing during radiosurgery. The objective of the present pilot study was evaluation of the interrelationships between changes in the skull size and variations in the normal brain radiation dose during GKS.

Materials and Methods

The conducted analysis was based on treatment data from 7 pediatric and 8 adult patients, who underwent GKS for management of epilepsy, a hypothalamic hamartoma, AVM, and a vestibular schwannoma (VS). In all cases,

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*,
Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_17,

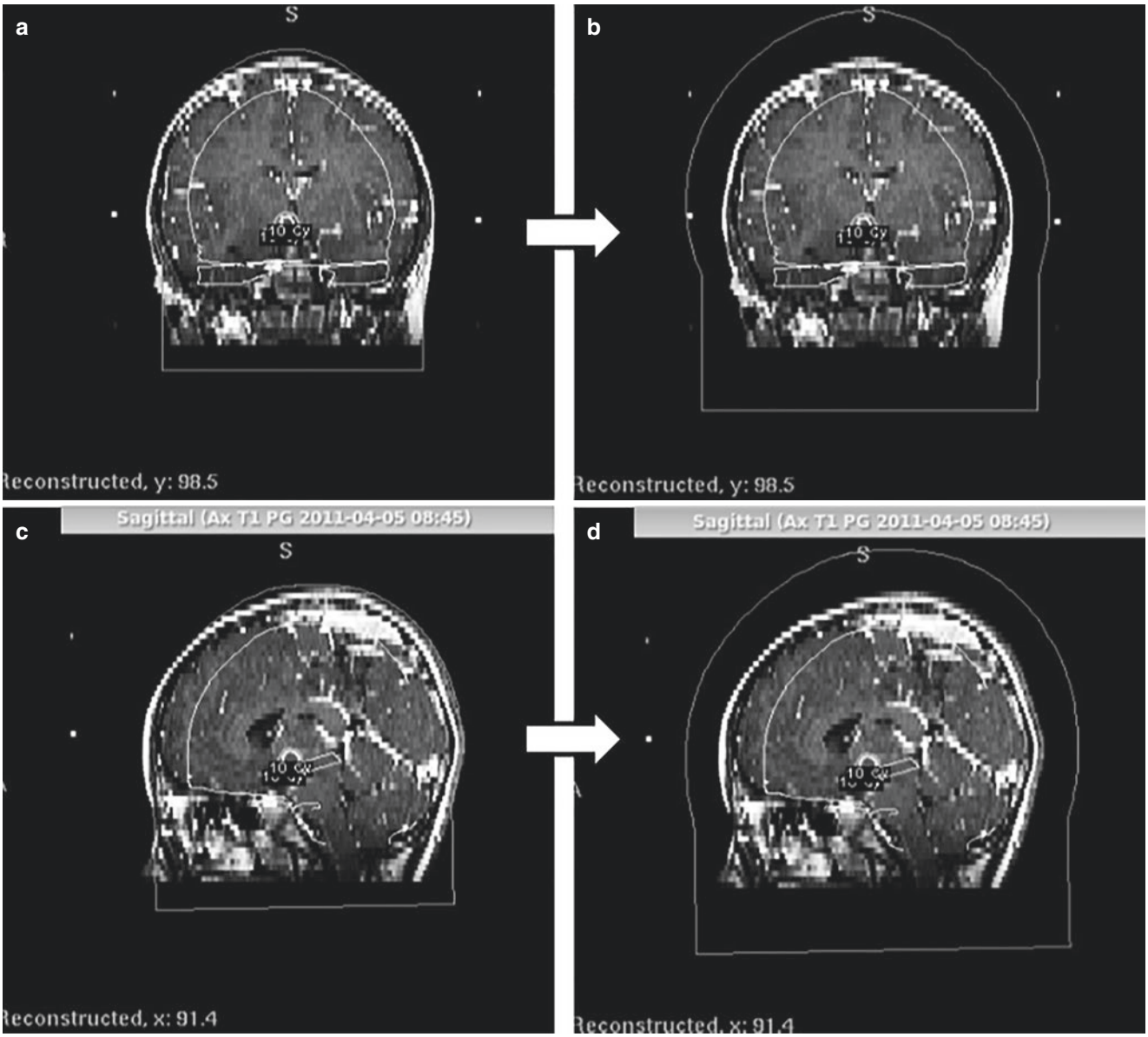

Fig. 1 Skull expansion modeling in the coronal (**a**, **b**) and sagittal (**c**, **d**) planes in a pediatric patient with a hypothalamic hamartoma treated with Gamma Knife radiosurgery. Negligible variations in the mean normal brain radiation dose and maximum point doses delivered to selected functionally important normal anatomical structures were noted in this case

radiosurgery was performed by means of Leksell Gamma Knife Perfexion™ (Elekta AB; Stockholm, Sweden) [7]. The target volumes ranged from 1.0 to 8.0 cc, and the prescription dose varied from 12.5 Gy (in the case of VS) to 24 Gy (in the case of epilepsy).

By use of systematic modeling within Leksell GammaPlan® (Elekta AB), in each analyzed case, the patient skull was "expanded" and "contracted" by variation of the skull measurement values from 0 to ±3 cm with an increment of 1 cm (Fig. 1). Corresponding to the skull size adjustment, the area of the normal brain was scaled using a previously reported method [8]. The mean normal brain radiation dose was then calculated for each variant of the adjusted skull size and compared with the original treatment plan to determine any potential trend in the changes. To minimize aliasing artifacts caused by partial volume effects, the mean brain dose (D) was computed according to the following formula:

$$\langle D \rangle = \frac{\oint_v Ddv}{V},$$

where the numerator is the three-dimensional dose D integrated over the entire normal brain volume V. In addition, variations in the maximum point doses delivered to functionally important normal anatomical structures—namely, the cochlea, brainstem, and anterior visual pathway (optic nerves and chiasm)—were also investigated for each variant of the adjusted skull size.

Results

With changes in the skull radius within ±3 cm, the maximum absolute deviation in the mean normal brain radiation dose for all 15 analyzed cases was 0.8% (Fig. 2). As the length of the skull radius increased, the mean normal brain radiation dose also increased linearly with a positive slope of 0.2% per centimeter of radius length change. According to the curve-fitting result ($R^2 > 0.999$), the confidence level for the positive slope was >99%.

The maximum point dose deviations in four assessed critical anatomical structures for all 15 analyzed cases did not exceed 0.5%, with an overall trend toward a dose increase in parallel with an increase in the skull radius (Fig. 3).

Discussion

Several previous physical studies investigated deviations in the radiation dose calculations associated with changes in the exterior skull contour, and it was noted that small random variations in the latter do not significantly impact dose computations [9–13]. In contrast to those reports, the present analysis evaluated whether relatively large changes (of up to several centimeters) in the skull size would significantly influence the mean normal brain radiation dose during GKS. The applied systematic modeling of "expansion" or "contraction" of the skull was aimed at simulating changes in its size during growth from infancy to adulthood.

The results showed that as the length of the skull radius increased, the mean normal brain radiation dose also increased linearly (confidence level >99%). From the physical point of view, this means that as the skull size increases, for each beamlet, the entrance dose contributes more to the mean brain dose (D) than the exit dose [14, 15]. Therefore, a small, but measurable, normal brain–sparing benefit is associated with relatively small skull sizes, which may be advantageous for pediatric patients undergoing GKS. To the best of our knowledge, such a finding has not been reported before. Additional investigations are needed to reveal whether observed variations in the normal brain radiation doses with regard to changes in the skull size are unique to the Gamma Knife or are also attributable to other radiosurgical modalities (e.g., a linear accelerator (LINAC)).

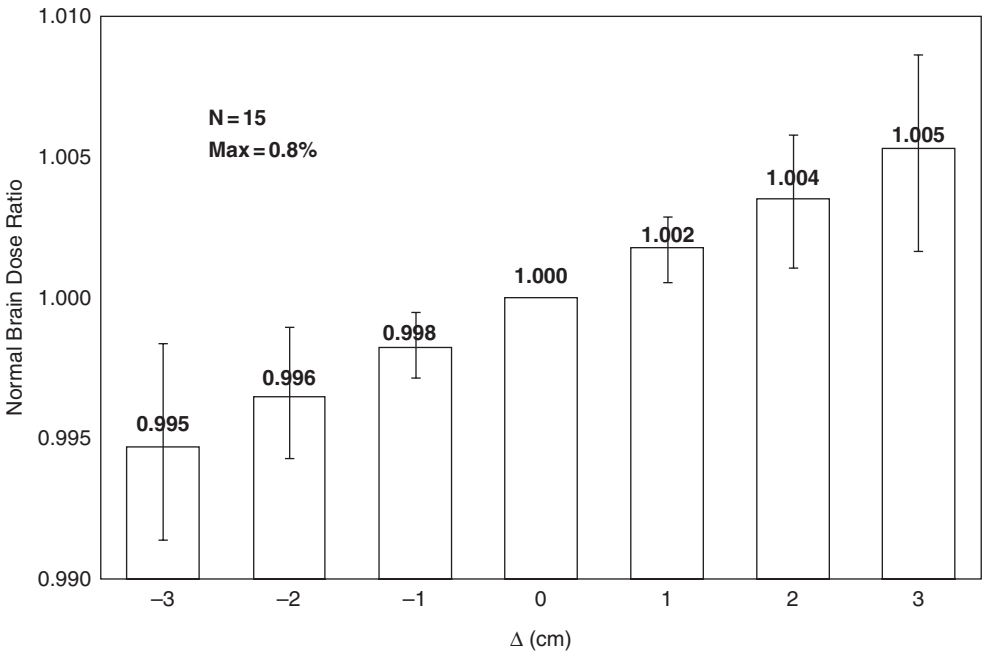

Fig. 2 Variations in the mean normal brain radiation dose (expressed as a ratio after comparison with the original treatment plan) with regard to changes in the skull radius (Δ) after modeling of its "expansion" or "contraction" in all analyzed cases (N). The *vertical bars* associated with each variant of the radius length indicate the data range. The maximum absolute deviation in the normal brain radiation dose was 0.8%

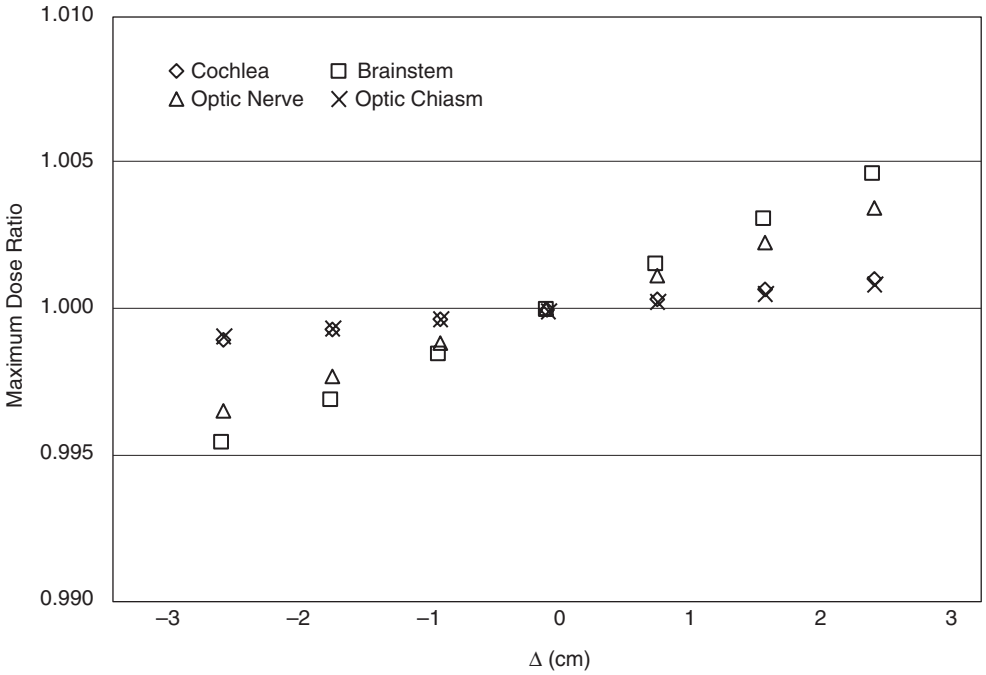

Fig. 3 Variations in the maximum point dose in the investigated functionally important normal anatomical structures (expressed as a ratio after comparison with the original treatment plan) with regard to changes in the skull radius (Δ) after modeling of its "expansion" or "contraction" in all analyzed cases. The maximum dose deviations did not exceed 0.5%, with an overall trend toward a dose increase in parallel with an increase in the skull radius

Conclusion

Systematic modeling of skull "expansion" and "contraction" has revealed that the normal brain radiation dose during GKS slightly increases in parallel with an increase in the skull radius. Therefore, the relatively small skull size of pediatric patients may be associated with dosimetric advantages in terms of normal brain sparing during GKS.

Conflict of Interest Dr. Ma has previously received an educational honorarium and travel support from Elekta AB. The other authors have no conflict of interest concerning the reported materials or methods. The updated results of this work have been presented during biannual meetings of the International Leksell Gamma Knife Society.

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Respiratory Monitoring During Gamma Knife Radiosurgery: Anesthesiological Aspects

Kotoe Kamata

Abstract Gamma Knife surgery (GKS) is a minimally invasive neurosurgical procedure, generally performed under moderate sedation along with local analgesia for fixation of a stereotactic frame to the patient's head, and is managed mostly by nonanesthesiologists. There are some risks for respiratory function during GKS and definite specifics for its management, since the presence of the stereotactic frame may impede access to the patient's airway and interfere with direct visual observation of him or her by medical personnel. Continuous monitoring for early detection of respiratory depression and timely intervention in the event of an emergency seem essential during radiosurgical procedures, but no relevant standards have been established to date. Since hypoventilation appears in advance of desaturation, sole monitoring of peripheral oxygen saturation (SpO_2) by pulse oximetry is insufficient for detection of an early respiratory decline. According to the American Society of Anesthesiologists (ASA) practice guidelines for sedation and analgesia by nonanesthesiologists, the adequacy of ventilation during moderate and deep sedation should be evaluated by continuous observation of qualitative clinical signs and monitoring of end-tidal carbon dioxide ($EtCO_2$). Overall, combined use of pulse oximetry and capnography may be recommended during GKS and may enhance its safety, especially in cases of medically fragile, uncooperative, or pediatric patients.

Keywords Anesthesiology · Capnography · Gamma Knife radiosurgery · Patient safety · Pulse oximetry · Respiratory monitoring

Introduction

With technical advances in different modes of minimally invasive treatment modalities, there has been a substantial growth in the numbers of diagnostic and therapeutic procedures requiring patient sedation outside the operating room (OR). Most of these cases are managed by nonanesthesiologists who are unfamiliar with details of procedural sedation and patient monitoring. This is particularly the case in Gamma Knife surgery (GKS), wherein minimal-to-moderate intravenous sedation and local analgesia are usually given to reduce discomfort and anxiety during attachment of a stereotactic frame to the patient's head and more or less prolonged irradiation.

According to the American Society of Anesthesiologists (ASA) practice guidelines for sedation and analgesia by nonanesthesiologists, the defining depth of sedation ranges from anxiolysis (minimal sedation) to general anesthesia, which differ in terms of the state of four main elements: responsiveness, the condition of the airway, spontaneous ventilation, and cardiovascular function [1]. During the procedure, the patient may progress to deeper level of sedation as sedative and analgesic requirements change proportionally to the intensity of the noxious stimulus. This is accompanied by increasing risks of complications, and airway obstruction, aspiration, respiratory depression with hypoventilation, apnea, and hypoxemia have all been suggested as principal causes of procedural sedation-related morbidity [2]. Of note, serious consequences of respiratory compromise are still not uncommon, as was evidenced by the Anesthesia Closed Claims Project analysis published in 2015 [3].

Although, physiologically, radiosurgery is significantly less invasive than microsurgical treatment of brain disorders, the potential risks for respiratory function and definite specifics of its management necessitate establishment of standards for monitoring during stereotactic irradiation.

K. Kamata (✉)
Department of Anesthesiology and Perioperative Medicine, Tohoku University School of Medicine, Miyagi, Japan
e-mail: macaroon@nifty.com

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*, Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_18,

This review focuses on details of respiratory monitoring during GKS from the viewpoint of the anesthesiologist.

Potential Risks of Gamma Knife Radiosurgery

GKS is categorized as a non-OR-setting neuroradiological and neurosurgical intervention, which requires repeated transportation of the patient between several sites located far from the main OR (e.g., the room where frame fixation is done, the magnetic resonance imaging (MRI) unit, the computed tomography (CT) unit, the angiography unit, and the radiosurgery unit). The treatment is typically performed by nonanesthesiologists during visual observation of the patient and conventional monitoring (e.g., electrocardiography (ECG), arterial blood pressure monitoring, and peripheral oxygen saturation (SpO_2) monitoring).

From the anesthesiological viewpoint, GKS is distinct from other types of non-OR-setting procedures—such as interventional radiology and cardiology, gastrointestinal endoscopy, or radiation therapy—because during radiosurgery, the patient is left alone in the radioactive area for a more or less prolonged period of time with a stereotactic frame fixed to his or her head. The stereotactic frame may interfere directly with upper airway patency. Moreover, rigid fixation of the frame for head immobilization during irradiation effectively eliminates neck movements. If required, releasing the frame fixation and placing a pillow under the patient's upper body may help to achieve an adequate sniffing position, but prompt direct intervention during ongoing radiosurgery generally remains impracticable, especially at the time of irradiation. In the event of an emergency, it may take up to several minutes to interrupt the procedure and enter the treatment room for direct patient observation and support.

Patient Monitoring During Sedation

In an attempt to standardize clinical practice and to minimize patient risks, several professional anesthesiological organizations have released standards and guidelines for procedural sedation [4]. These universally state requirements for assessment of the sedation level, arterial pressure measurement, and pulse oximetry. Since the responses of an individual patient to administered sedatives are difficult to predict, at the transition from moderate to deep sedation, capnography for continuous monitoring of ventilation is also recommended. It is widely accepted that drug administration should be minimized with consideration of the required depth of sedation, but even subhypnotic doses of sedatives may cause significant pharyngeal dysfunction [5], which readily leads to aspiration. Since GKS has specific risks in terms of timely respiratory management, early detection of inadequate respiratory status is imperative for initiation of interventions to prevent sedation-related morbidity [6].

The provider of anesthesia should periodically evaluate the level of sedation throughout the procedure. Deaths from outpatient office–based interventions have been reported—in particular, in patients who experienced respiratory or circulatory arrest, presumably due to oversedation [7]. Several scales have been adopted to assess the level of sedation through evaluation of responsiveness to verbal and tactile stimulation; the most widely accepted ones include the ASA Continuum of Depth of Sedation, the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Scale, and the Ramsay Sedation Scale. However, their practical application may disturb sedation, since the patient should be stimulated at the time of each assessment. In such circumstances, electroencephalography (EEG) monitoring may be more beneficial, but (to the best of the author's knowledge) there has been only one study clearly demonstrating its positive impact on patient safety during procedural sedation. In 2014, Yang et al. [8] reported that in comparison with standard care, EEG-guided nurse-administered moderate sedation using midazolam and fentanyl does not reduce drug consumption but results in a significantly lower incidence of pronounced desaturation.

Assessment of Respiratory Status

Respiratory status is determined by two main elements: respiration and ventilation. Since early detection of respiratory abnormalities allows a rapid response to prevent sedation-related morbidity, several methods have been developed for clinical evaluation of respiratory function (Table 1). Clinical observation is considered to be the simplest technique. However, as was reported by Vargo et al. [9], during procedural sedation for 49 upper gastrointestinal endoscopies, 54 episodes of apnea were detected in 28 patients by capnography, 27 by pulse oximetry, and none by visual assessment. Traditional electrical impedance respiratory rate monitoring is unable to distinguish respiratory effort and respiratory flow. The parameters of transcutaneous carbon dioxide (CO_2) monitoring correlate well with the measured partial pressure of CO_2 in arterial blood ($PaCO_2$), but it is less effective for detection of apnea. Clinical application of acoustic monitoring, which evaluates turbulent airflow in the larynx, has been encouraging and has high sensitivity in detecting pauses in ventilation. Nevertheless, at present, the main methods used clinically for assessment of respiratory function are pulse oximetry and capnography.

Table 1 Methods for evaluation of respiratory function during procedural sedation

Method	Main advantages	Main disadvantages
Clinical observation	Simplicity	Limited reliability
Pulse oximetry	Accurate detection of SpO_2	Cannot evaluate alveolar ventilation; delays in detecting hypoventilation in oxygenated patient
Capnography	Sensitivity in detecting respiratory depression	Sampling delay; possibility of sampling tube occlusion
Impedance monitoring	Concurrent use of ECG	Cannot distinguish obstructive apnea
Transcutaneous CO_2 monitoring	Good correlation with $PaCO_2$	Less effective in detecting apnea
Acoustic monitoring	High sensitivity in detecting pauses in ventilation	Inappropriate for use during neck surgery

ECG electrocardiography, *$PaCO_2$* partial pressure of carbon dioxide in arterial blood, *SpO_2* peripheral oxygen saturation

Pulse Oximetry

Pulse oximetry measures SpO_2 and expresses it as a percentage. Although this technique can only indirectly evaluate oxygenation of the peripheral blood, it has received widespread acceptance (particularly among nonanesthesiologists involved in non-OR-setting procedures) as a sole method for respiratory monitoring because of its ease of use, simplicity of data interpretation, ready availability, and relatively low cost, in addition to the lack of effective alternative modalities. However, it has been suggested that pulse oximetry alone is inadequate for assessment of respiratory function during endoscopic procedures under sedation with oxygen administration, because of the delay in detecting alveolar hypoventilation [10]. In fact, a fully preoxygenated healthy adult or adolescent can tolerate, on average, 6 min of apnea before developing oxygen desaturation (SpO_2 <90%) [11]; therefore, pulse oximetry cannot accurately reflect alveolar hypoventilation, apnea, or airway obstruction when supplemental oxygen is provided. Since desaturation is a late sign of inadequate ventilation, monitoring of alveolar ventilation during sedation has been recommended consistently.

Capnography

Capnography is another commonly used method and evaluates changes in the partial pressure of CO_2 in the inspired and expired gases during the respiratory cycle. This noninvasive monitoring technique closely approximates $PaCO_2$ and thus allows evaluation of alveolar ventilation [12]. A large meta-analysis of procedural sedation indicated that respiratory depression is 17.6 times as likely to be detected when capnography is added to conventional monitoring (a combination of pulse oximetry and visual assessment of chest wall movements) [13]. It has also been reported that additional capnography monitoring reduces the incidence of arterial oxygen desaturation (defined as a fall in SaO_2 of ≥5% compared with baseline or any fall to the values <90%), as well as moderate and severe hypoxemia (SaO_2 <90% and ≤85%, respectively) during colonoscopy under propofol sedation, as it triggers early airway management [14].

Theoretically, changes on capnography may forewarn of respiratory depression in any case of hypoxia. However, the obtained tracings of spontaneous breathing cannot be assessed quantitatively, since the recorded end-tidal CO_2 ($EtCO_2$) does not correlate well with $PaCO_2$, as it does during artificial ventilation [15]. Therefore, if the patient's natural airway is maintained during procedural sedation, it is absolutely necessary to compare the obtained $EtCO_2$ values with the baseline level and assess the waveform shape and respiratory rate [12]. Relative $EtCO_2$ changes of >10 mmHg in comparison with baseline and/or depression or loss of the capnography waveform may indicate significant respiratory dysfunction [16]. According to several reports, the median time interval between capnographic evidence of respiratory depression and hypoxia ranges from 60 s to 262 s [9, 17–20], which may be sufficient for early initiation of treatment, allowing prevention of sedation-related complications—in particular, during GKS.

Nevertheless, the effectiveness of capnography in early detection of hypoxemia caused by hypoventilation during procedural sedation—in particular, in patients receiving supplemental oxygenation—still requires clarification, since the reported results have been controversial and the benefits of such monitoring have not been confirmed consistently. For example, van Loon et al. [21] conducted a randomized controlled trial in healthy adult women who underwent minor elective gynecological procedures under deep sedation with propofol (given by a nonanesthesiologist) and did not receive supplemental oxygen routinely. Out of 427 enrolled patients, 209 had standard respiratory monitoring with pulse oximetry and visual assessment of their breathing pattern, whereas in another 206 patients, additional capnography was used. There was no difference in the incidence of hypoxemia (defined as SpO_2 <91%) between the two cohorts of patients (24.9% versus 25.7%) [21].

Conclusion

GKS is widely accepted as a minimally invasive modality for management of various intracranial disorders. However, such treatment may carry potential risks because during irradiation, the patient is left alone for a more or less prolonged

period of time with rigid fixation of his or her head within a stereotactic frame. This may potentially decrease the safety of the radiosurgical procedure, especially in cases of medically fragile, uncooperative, or pediatric patients. From the anesthesiological point of view, the main problems in such a situation may be caused by airway collapse and inability of medical personnel to intervene immediately in the event of an emergency. Therefore, the patient's physical condition—in particular, their respiratory status—should be carefully evaluated before GKS in all cases, even if procedural sedation is not planned. Continuous respiratory monitoring during radiosurgical treatment by means of both pulse oximetry and capnography may help to avoid undesirable side effects and complications caused by depression of respiratory and ventilatory functions.

Acknowledgments The author thanks all the staff of the Gamma Knife Unit and the Department of Anesthesiology of Tokyo Women's Medical University for their great aid, and especially Dr. Makoto Ozaki (Department of Primary Care Medicine, Nishiarai Hospital), who provided for me an invaluable help since this clinical project was planned and initiated. Indeed, this work could not be accomplished without his kind support and important suggestions. Also, special thanks are due to Drs. Motohiro Hayashi, Noriko Tamura, Ayako Horiba, Kentaro Chiba, Yasuo Aihara and Takakazu Kawamata (all from Department of Neurosurgery, Tokyo Women's Medical University) for their constant professional cooperation.

Conflict of Interest The author has no conflict of interest concerning the reported materials or methods.

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The Proud History of Psychosurgery in the USA

Joseph Galante and Michael Schulder

Abstract To understand the development and growth of psychosurgery, the context of psychiatric care in the mid-twentieth-century USA must be considered—for example, overpopulation and understaffing of public institutions, and typical use of psychotherapy, which was generally useless in treating the symptomatology of severe mental illness. Therefore, the introduction of prefrontal lobotomy (and, later, transorbital lobotomy) by Drs. Walter Freeman and James Watts, who modified the technique of leukotomy developed by Nobel Prize laureate Dr. Egas Moniz, was considered revolutionary and quickly gained widespread acceptance by medical community. No other alternative treatment at the time demonstrated comparable efficacy. At its peak, psychosurgery was sometimes applied inappropriately, but records from multiple institutions across the USA demonstrate that these were exceptional cases, whereas, as a rule, selection of surgical candidates was based on very strict criteria, indicating the high professionalism and humanity of medical staff. Although psychosurgery has declined heavily since the 1950s, it is not obsolete and is currently considered a valuable treatment option, realized through various open, stereotactic, or radiosurgical procedures.

Keywords Egas Moniz · Frontal leukotomy · Gamma Knife capsulotomy · History of neurosurgery · James Watts Prefrontal lobotomy · Psychosurgery · Transorbital lobotomy · Walter Freeman

J. Galante
Department of Neurosurgery, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

M. Schulder (✉)
Department of Neurosurgery, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

Brain Tumor Center, Northwell Neurosciences Insitute, Lake Success, NY, USA
e-mail: mschulder@northwell.edu

Introduction

Lobotomy: a word that evokes crude images of maniacal doctors, negligent public institutions, and failed treatment in the court of public and professional opinion. Questions of efficacy and the ethics of psychosurgery seem clear cut to professionals in modern medicine—in particular, psychiatry and neurosurgery. However, if we look through the lens of physicians of the 1930s through the 1950s, along with hospital staff and families who helplessly saw people they cared for languish in the throes of serious mental illness, things are less black and white. To understand the development and growth of psychosurgery, we must consider the context of psychiatric care in the mid-twentieth-century USA. Large institutions that covered hundreds of acres were filled beyond capacity, medications to treat severe psychiatric symptoms were virtually nonexistent, societal acceptance of mental illness was not a consideration, and physicians were rendered powerless against diseases that hospitalized staggering numbers of patients (e.g., 528,239 individuals in 1955, out of a total US population of approximately 164,000,000) [1]. When taking into consideration these factors, we should hesitate to look down our twenty-first-century noses at lobotomy and its related methods. These were procedures that provided hope to patients and families who otherwise had none.

Public Psychiatric Care at the Time

To look again at that year of 1955, only around 100,000 people out of the entire US population had private insurance, and few could afford private psychiatric care at the time [2, 3]. The great majority of mentally ill individuals who required inpatient hospitalization found themselves at a public institution where services ranged from acute to chronic care [1, 4].

M. F. Chernov et al. (eds.), *Gamma Knife Neurosurgery in the Management of Intracranial Disorders II*, Acta Neurochirurgica Supplement 128, https://doi.org/10.1007/978-3-030-69217-9_19,

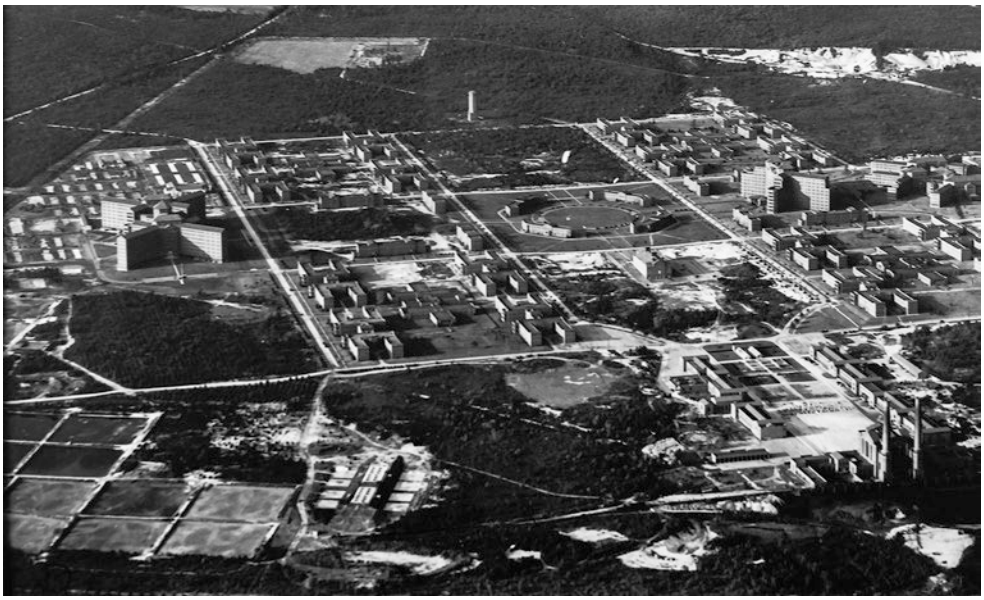

Fig. 1 Aerial view of Pilgrim State Hospital (Brentwood, NY, USA) in 1954

Pilgrim State Hospital, located in Suffolk County, Long Island, was built to care for 10,000 of New York City's mentally ill but grew to a peak patient population of 13,875 on 825 acres of land in 1954 (Fig. 1) [5]. Approximately 270 miles to the north of Pilgrim State Hospital sits Utica State Hospital, whose population in 1952 was 2083 at a facility rated for 1444 patients [6]. Willard State Hospital, located on the shores of Seneca Lake, was New York State's hospital to house and treat chronic cases of mental illness, with a 1954 census of 3053 at an institution certified for 2431 patients [7]. This was the story of public institutions across the USA at the time: overpopulation and understaffing, with the chief treatment being psychotherapy, which proved futile in treating the symptomatology of severe mental illness.

Development of Prefrontal Lobotomy

Dr. Egas Moniz, a neurologist, and his neurosurgeon associate Dr. Almeida Lima performed their first frontal leukotomy in 1935 and twenty more procedures on persistently mentally ill patients in Portugal in the following year. Moniz's leukotomy aimed to divide white matter tracts connecting the prefrontal cortex and thalamus during an open psychosurgical procedure [8]. In 1949, Moniz received a Nobel Prize in Physiology or Medicine for this work.

Dr. Walter Freeman, an American neurologist at St. Elizabeth's Hospital in Washington, DC, was aware of the results Moniz had reported on leukotomy. At the age of 28, in 1934, Freeman was the youngest laboratory director employed by this institution of 5000 patients. At St. Elizabeth's, he observed the anguish of serious and relentless mental illness. Freeman modified the leukotomy procedure into what he labeled prefrontal lobotomy, an open ablative surgery similar to leukotomy (but arguably more destructive). After many cadaver studies, Freeman and his neurosurgical partner Dr. James Watts performed their first lobotomy in 1936 at George Washington University Hospital in Washington, DC [9]. The patient, Mrs. Alice Hood Hammat, was a housewife from Topeka (KS, USA), who suffered from chronic anxiety, depression, and insomnia; she sought relief from her symptoms from Dr. Freeman. Her surgery proved efficacious, as she was able to remain out of a psychiatric hospital, noted reduced anxiety, and was less depressed. Additionally, her husband reported being pleased with the results of the lobotomy, describing his wife as seemingly happy for the next 5 years until her death from pneumonia at the age of 68 years. Alice herself did not disagree with the description of her leading a better life after the operation; she also reported to Freeman that she no longer had suicidal ideation and she enjoyed social interaction with friends and the ability to leave her home for extended periods of time [10].

Results of Prefrontal Lobotomy

Freeman and Watts published their findings on 200 lobotomy cases in 1942 and reported not only their surgical successes but also the related perioperative morbidity. They stated that 63% of the patients had an improvement in symptoms, 23% had no change at all, and 14% were considered worse off or died from surgical complications [9]. At Fairfield Hills State Hospital (Newtown, CT, USA), 107 chronically mentally ill patients underwent prefrontal lobotomy between 1946 and 1949. Few complications associated with the surgery, other than convulsions, were reported. The best results were noted in nonschizophrenic and paranoid schizophrenic patients,

with an overall improvement rate of 57.6%, similar to the findings from lobotomy reported by Freeman and Watts. The physicians noted that 37% of those patients were discharged from the state hospital during the 3 years of the study—a remarkable result for individuals whose caregivers expected to spend their entire lives hospitalized [11]. In England, a review of 10,000 prefrontal lobotomies that took place between 1943 and 1954 concluded that 70% of the patients experienced an improvement in their psychiatric condition after the operation (with 18% returning to "normal life") and reported a 6% mortality rate [12]. In 1951, a study at Wernersville State Hospital in rural Berks County (PA, USA) showed that out of 102 lobotomized patients, 25 were discharged from the state hospital, with 15 deemed to have had a total remission (Fig. 2). An overall recovery rate of 75% was reported, with a 1.96% mortality rate [13]. In 1952, 45 patients underwent prefrontal lobotomies at Utica State Hospital, with favorable results. One operated patient died from a heart attack unrelated to psychosurgery, and five patients were discharged from the hospital that year [6]. Thus, lobotomy had the attention of professionals in psychiatric medicine, as no other alternative treatment at the time was demonstrating durable success in patients with chronic or persistent symptomatology (Fig. 3) [8].

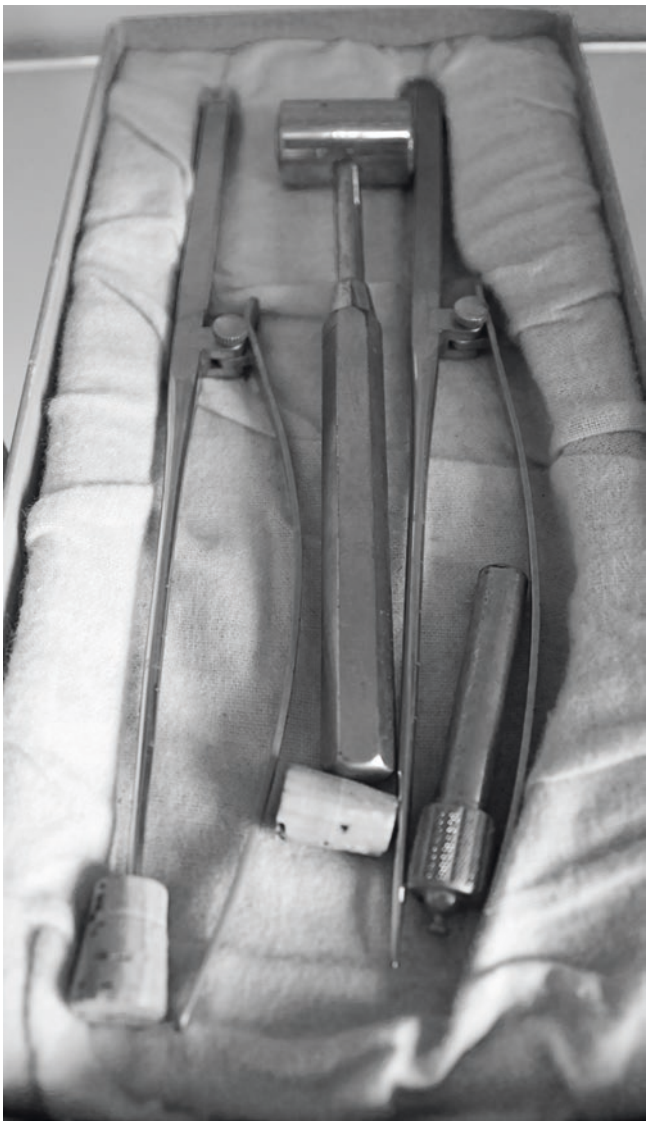

Fig. 2 "Orbitoclasts" used during transorbital lobotomy at Wernersville State Hospital (Wernersville, PA, USA)

Patient Selection for Psychosurgery

Contrary to common belief, patients were not arbitrarily selected for psychosurgery, nor was it applied punitively. Large studies were conducted at many public institutions in the USA, reporting information that was statistically congruent.

The selection criteria for prefrontal lobotomy at Fairfield Hills State Hospital included a long documented duration of mental illness (mean 7.4 years), continuous hospitalization (mean 4.4 years), and active symptoms. All patients had previously been refractory to somatic treatments such as electroconvulsive therapy (ECT) and other forms of shock therapy [11]. In New York, where Willard State Hospital primarily cared for chronic patients, one might have expected to find a large number of lobotomies performed if we apply popular theories of its arbitrary use. Of the 2955 patients admitted in 1952, 410 received ECT and one received insulin coma therapy, but not a single patient underwent lobotomy that year [3]. Considering the volume of patients in an institution that utilized psychosurgery, it is logical to conclude that physicians did not feel they had a suitable candidate for a surgical procedure. At Pilgrim State Hospital in 1951, 353 prefrontal lobotomies were performed out of a patient population of 12,951. The report of the resident physician from that institution describes a careful selection process in patients who were refractory to previous treatments, plans for a 5-year follow-up study of each operated individual, and regular surveys of lobotomized patients, to be conducted both in the hospital and after discharge [14]. At Utica State Hospital in 1952, prefrontal lobotomies were performed in selected patients who were refractory to ECT, insulin coma therapy, and other somatic treatments [6]. The aforementioned study of 102 lobotomized patients, performed in 1951 at Wernersville State Hospital, also indicated that strict criteria were adhered to in consideration of candidates for surgical intervention. Being refractory to all viable therapeutic and somatic treatment modalities of the day, and having persistent mental illness, were requirements for eligibility [13].

These reports are typical of the time and contradict the seemingly axiomatic notion that psychosurgery was used indiscriminately across the public care system. Overcrowding in these institutions was not synonymous with a lowered standard of care or lack of medical professionalism and humanity (Figs. 4, 5, 6).

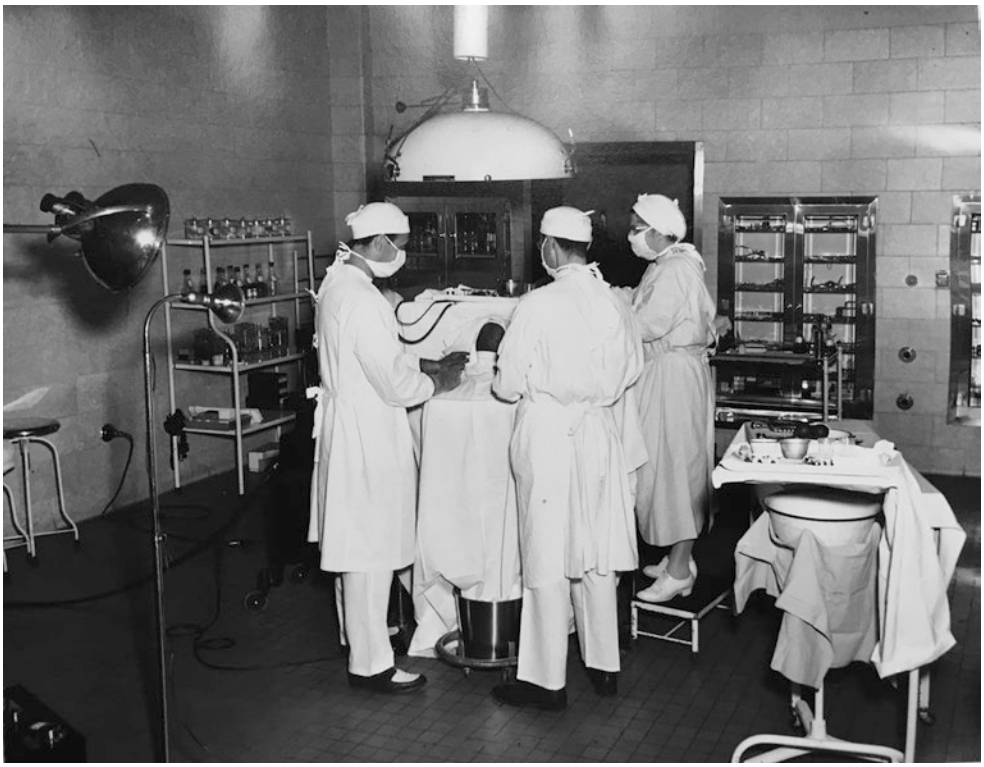

Fig. 3 Surgical preparation for prefrontal lobotomy at Pilgrim State Hospital (Brentwood, NY, USA) in the 1940s

Fig. 4 Potato sack race at Hudson River State Hospital (Poughkeepsie, NY, USA) in 1949

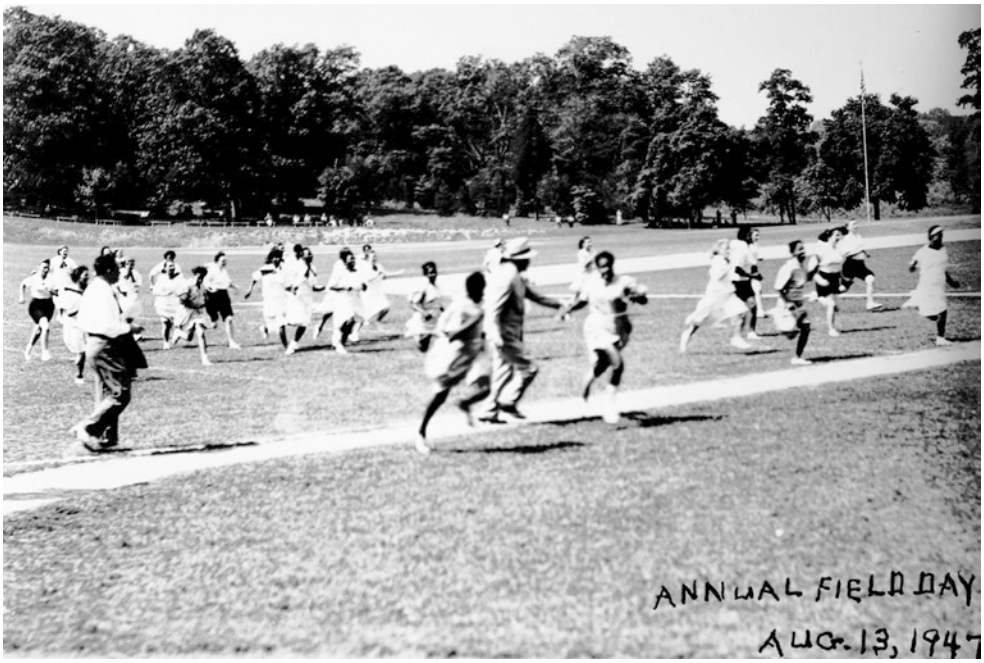

Fig. 5 Field day at Kings Park State Hospital (Kings Park, NY, USA) in 1947

Fig. 6 Christmas celebration in the adolescence ward at Central Islip State Hospital (Brentwood, NY, USA) in the 1940s

Further Technical Developments: From Transorbital Lobotomy to Stereotaxis

Moving back to 1945, with influence from the leukotomy techniques developed by the Italian psychiatrist and neurosurgeon Dr. Amarro Fiamberti, Freeman began to advocate a closed (or what we might now call "minimally invasive") procedure to generate lesions in the frontal lobe. Mrs. Sallie Ellen Ionesco was a 29-year-old housewife in 1946. She suffered from depression and attempted to kill herself and to

smother her own child. She visited Freeman in his Washington, DC, office, becoming the first patient to undergo transorbital lobotomy. She was rendered unconscious by ECT, and, following the shock, an "orbitoclast" was inserted at the base of the frontal lobe and swept 15 degrees laterally in each ocular orbit [15]. After her surgery, Sallie was described by her family as nonviolent and living a relatively normal life until her death in 2007. In an interview, Sallie praised Freeman and stated her favorable thoughts on the procedure [9].

Watts, however, was skeptical of transorbital lobotomy and, by 1950, had parted ways with Freeman. Despite this separation, transorbital lobotomy spread to public institutions nationwide and was viewed in a favorable light in treating patients requiring permanent custodial care. By that time, lobotomy had gained the respect of physicians around the world and was considered a legitimate psychosurgical procedure. Some 60,000 psychosurgeries were performed in the USA and Europe between 1936 and 1956 [15]. By 1952, the physiologist John Fulton was urging a transition from transorbital lobotomy to stereotactic methods that could produce precise and replaceable lesions in the frontal lobe, setting the stage for anterior cingulotomy, subcaudate tractotomy, and deep brain stimulation (DBS)—all part of modern neurosurgical practice.

The Dark Side of the Story

In those days, society was looking for a fast cure for mental illness, and physicians were trying to improve the quality of life for patients in ways big or small. The disjointed goals of the public and professionals contributed to tension surrounding the lobotomy procedure. Freeman played a significant part in the development of psychosurgery, becoming a topic of media interest. He made it his business to build relationships with well-established newspapers and magazine writers, to whom he touted the success that lobotomy had in ameliorating symptoms. This was done prematurely without ample study of the undesirable effects of the procedure and against the advice of the medical community [16]. Images of "ice pick lobotomies" were viewed unfavorably by the public. Freeman openly invited the press to view his transorbital procedures, and, in one case, a patient died during the surgery in front of reporters.

Books in the 1960s, such as *One Flew Over the Cuckoo's Nest*, depicted institutions as oppressive warehouses where patients were held against their will and operated on as a punishment. This was a far cry from the state of affairs in state hospitals. (In)famous cases such as that of Rosemary Kennedy, who had a mild developmental delay and underwent lobotomy at the persistent behest of her father, furthered the villainization of both Freeman and psychosurgery [16].

The Decline of Psychosurgery

A new era in psychiatry began in 1955, with the advent of chlorpromazine (also widely known under the trade name Thorazine), which was sold as a tranquilizer to state hospitals. Of interest, it was commonly marketed as a "chemical lobotomy" without complications. Nevertheless, soon after its introduction, side effects of chlorpromazine—such as pseudoparkinsonism, tardive dyskinesia, and even death—were encountered not infrequently until proper dosing routines were established and addition of mood-stabilizing anticonvulsants was considered.

Although psychosurgery has declined heavily since the 1950s as a result of the advent of medical treatment options (Fig. 7), it is not obsolete and is still applied in severe and refractory cases. Moreover, during the late 1990s, the use of DBS to treat psychiatric disorders was introduced, which led to re-evaluation of the benefits of psychosurgery. Modern procedures utilize stereotactic or radiosurgical methods, while producing precise, repeatable, and uniform lesions via minimally invasive techniques. In particular, Gamma Knife capsulotomy has revealed significant benefits (especially during long-term follow-up) for patients with obsessive–compulsive disorder (OCD) and, possibly, major depressive disorder (MDD) as well [17].

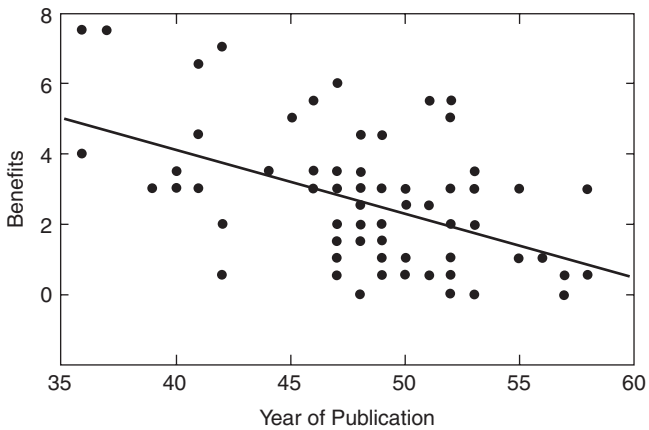

Fig. 7 Correlation between the number of benefits from lobotomy listed per article and the year of publication. (Adapted from Diefenbach et al. [16])

Conclusion

There is a final thought to consider with respect to Walter Freeman and his life's work: was he a mischievous man satisfying a desire for fame and ego, or a doctor dedicated to the treatment of people tormented by illness that society had devalued and hidden away from public view with no hope of a return? Freeman spent the remainder of his life interviewing the patients he had operated on, reporting both improvements and complications that resulted from the operation. He kept exceptionally detailed notes and published one last report in 1971, which outlined his findings in detail.

This is not just the story of Walter Freeman and his career but the story of American psychosurgery, misremembered and branded with a black mark on the medical community, never to be examined again. Sensational press and Hollywood's perpetuation of evil institutions harming patients with ice picks are still predominant in the minds of millions. It would be romanticizing to deny or ignore that at the height of its use, psychosurgery was sometimes applied inappropriately, but, in truth, those would be exceptions to the historical rule. There is debate on the precise number of patients and the degree to which lobotomy helped or harmed them. There is, however, no question that psychosurgery was not abused on a large scale but was widely utilized as a last resort in the most severe cases of those individuals, who had no hope of a life free of anguish. The same selection criteria are applied today when psychiatric surgery is being considered as a valuable treatment option realized through various open, stereotactic, or radiosurgical procedures.

Conflict of Interest The authors have no conflict of interest concerning the reported materials or methods.

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Subject Index

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