CyberKnife Stereotactic Radiosurgery for Intracranial Neoplasms, with a Focus on Malignant Tumors

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Stereotactic radiosurgery is well established as a means of managing intracranial tumors, both as an adjuvant to surgical resection, and also as a primary treatment modality for those tumors that are considered unresectable by conventional surgical means. Of particular concern during radiosurgery of brain tumors is the risk of radiation damage to otherwise healthy tissue, potentially resulting in cognitive impairment. The conformality and precise targeting of the CyberKnife radiation beam enables this risk to be minimized to a greater extent than hitherto possible, which may allow treatment to be completed in a small number of fractions, thereby improving the quality of life for patients. The CyberKnife has proven particularly valuable in the treatment of metastases, which represent the great majority of brain tumors, though its role in the management of malignant glial tumors remains a subject of controversy. This article reviews the published studies on the efficacy of CyberKnife radiosurgery for brain tumors of both glial and metastatic origin, and considers its future role in the management of such lesions.

Key words: CyberKnife; Stereotactic radiosurgery; Glioblastoma; Astrocytoma; Brain metastases; Melanoma.

Introduction

Radiation therapy has played an important role in the management of brain tumors for several decades, and has been shown to prolong survival of both primary and secondary neoplasms of the central nervous system. While whole brain radiation therapy (WBRT) has traditionally been the standard modality for treating unresectable brain tumors, the sensitivity of the nervous system to radiation (1) is such that WBRT inevitably results in damage to healthy neural tissues. Therefore, when metastases are limited in number and extent, it is preferable to use more focused external beam radiation therapy (EBRT) delivered using a precisely directed linear accelerator (LINAC). WBRT remains an important means of controlling metastases, however, and as explained below has been shown to be particularly effective when combined with stereotactic radiosurgery. Unfortunately, even focused EBRT delivered via LINAC still results in significant irradiation of healthy neural tissue in the path of the beam, resulting in a significant risk of neuropsychological and cognitive impairment in long-term survivors (2) and children (3), and this has promoted interest in the development of new treatment paradigms.

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Abbreviations: CKSRS: CyberKnife stereotactic radiosurgery; CT: Computed tomography; EBRT: External beam radiation therapy; FFP: Freedom from progression; Gy: Gray (the SI unit of absorbed radiation dose); RPA: Recursive partitioning analysis; RTOG: Radiation Therapy Oncology Group; SRS: Stereotactic radiosurgery; WBRT: Whole brain radiation therapy.

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of stereotactic radiosurgery (SRS) techniques with a view to replacing EBRT where possible. In SRS, the radiation is focused even more tightly onto brain tumors while sparing as much of the surrounding tissue as possible, thereby minimizing undesirable sequelae. The use of stereotactic radiosurgery (SRS) for both primary and metastatic brain tumors has been extensively researched and reviewed (4, 5, 6, 7, 8, 9, 10, 11, 12, 13) and multicenter protocols have been conducted to investigate whether radiosurgery should partly or wholly replace other forms of irradiation, particularly for metastatic tumors.

An early randomized clinical trial (14) compared local control in patients with 2-4 metastases who underwent either wholebrain radiotherapy (WBRT) alone or WBRT and SRS. The trial was halted after 60% accrual because the interim analysis showed a significant advantage to adding SRS. Median time to local failure was 6 months in patients who received WBRT alone, versus 36 months in patients who received both WBRT and SRS.

The most influential study of the use of radiosurgery to treat brain metastases is probably the Radiation Therapy Oncology Group protocol RTOG 95-08 (15), a multi-institutional trial in which 333 patients with 1-3 metastases were randomly assigned to two treatment groups: those in one group underwent both SRS and WBRT, while those in the other group underwent WBRT alone. With survival as the primary criterion, it was found that the two groups that benefited from SRS were those with a single metastasis, regardless of recursive partitioning analysis (RPA) class, and those in RPA Class 1 with up to 3 metastases. (It should be noted that that 31 of 164 patients assigned to the SRS group did not actually undergo SRS, while 28 of 167 patients in the WBRT group received salvage SRS, so the actual survival advantage with SRS was even more marked.) On the basis of this protocol, SRS has become established as an important tool in the local management of brain metastases.

The value of SRS in treating primary gliomas, and in particular glioblastoma multiforme, is less clear-cut. A study by Kondziolka et al. (6) evaluated 64 patients with glioblastoma multiforme and 43 patients with anaplastic astrocytoma who were treated with SRS, and found a survival advantage compared to historical controls. However, an extensive study (RTOG 93-05) (9) of 203 patients with newly diagnosed malignant gliomas showed no apparent advantage in terms of survival or quality of life when SRS was used in conjunction with EBRT and carmustine (BCNU) to treat supratentorial glioblastomas. The issue is further complicated by the observation that SRS-eligible patients often have prolonged survival independent of treatment (16). Even so, there are advantages to using CyberKnife over older forms of SRS as employed in the RTOG 93-05 protocol.

This article primarily reviews the published use of Cyberknife stereotactic radiosurgery (CKSRS) in the management of brain tumors and does not address the larger question of the potential of stereotactic radiosurgery as an alternative to external beam irradiation techniques.

**CyberKnife Versus Conventional Approaches to Radiosurgery**

**Advantages of CyberKnife in Treating Tumors**

In contrast to EBRT, which may involve dozens of treatment sessions over many weeks, CKSRS can often be accomplished with a smaller number of high-energy doses. The non-isocentric radiation beam projected by the CyberKnife enables it to provide localized focused radiation treatment without the associated morbidity that frequently arises from conventional radiotherapy. The highly conformal nature of the beam is particularly valuable in achieving precise irradiation of irregularly shaped tumors: Large treatment doses can be sub-divided into multiple stages or fractions (typically two to five) to spare healthy tissue adjacent to the tumor. This option for fractionation is also advantageous as an adjuvant treatment for patients who have already undergone and failed extended courses of conventional radiotherapy, or those whose tumors are in critical regions of the brain. In addition to its high conformity, the CyberKnife has been demonstrated to possess sub-millimetric accuracy (17), further minimizing the risk to healthy tissue.

While frequently employed as adjuvant therapy following surgical resection (4, 10), radiosurgery is also of value in treating tumors that are deemed inoperable by conventional surgical techniques. Such inoperability may result from their location in critical areas of the brain, or from their diffuse margin that makes a surgical excision impossible due to invasion of normal tissue. A classic example of such use is in the management of tumors of the cerebellopontine angle such as acoustic neuromas, the surgical management of which often results in damage to either the seventh or eighth cranial nerve. By arresting further growth through the use of radiosurgery these tumors can often be brought under long-term control without incurring the risk of deafness or facial palsy associated with surgical excision (18). One particular benefit of radiosurgery administered in a hypofractionated technique employing the CyberKnife instead of through a single fraction using frame-based radiosurgery is that the preservation of function of these nerves may be enhanced through fractionation (19, 20).

**Frameless Versus Frame-based Approaches to Brain Tumors**

In addition to the advantages inherent in the non-isocentric beam and its demonstrated precision, the CyberKnife is the...
first radiosurgery device that is able to deliver precisely targeted doses to intracranial sites without requiring installation of a stereotactic frame to provide a rigid reference coordinate system. As such frames are normally fixed directly to the patient’s skull by means of titanium or aluminum screws driven into the bone, the use of a frameless system like the CyberKnife offers a significant improvement in pre- and post-procedural comfort for the patient, with no potential for bleeding or infection. Even when SRS is performed with the assistance of a non-invasive frame, the patient must still be immobilized for the duration of the procedure, whereas this is not necessary with the CyberKnife. Similarly, in the absence of invasive procedures, neither general nor local anesthesia is normally required at any stage during treatment.

The CyberKnife offers several advantages for pediatric patients with tumors that are amenable to SRS: in addition to avoiding the risk of cognitive decline associated with WBRT (3), use of the CyberKnife permits SRS to be performed on young children whose thin skulls preclude the fixation of a stereotactic frame, and in many cases the radiosurgery can be performed without the need for general anesthesia. Giller et al. (21) reported the results of a series of 21 pediatric patients (age: 8 months to 16 years) with unresectable tumors. Tumors comprised 3 pilocytic astrocytomas, 2 anaplastic astrocytomas, 3 ependymomas (2 of which were anaplastic), 4 medulloblastomas, 3 atypical teratoid/rhabdoid tumors, 3 craniopharyngiomas and 3 other pathologies. Using a mean marginal dose of 18.8 ± 8.1 Gy, local control was achieved in all 5 patients with astrocytomas, in 3 of those with medulloblastomas and in the 3 with craniopharyngiomas. Twenty-seven of the treatments (71%) were delivered as a single fraction, and 8 of the patients (38%) did not require general anesthesia.

**CyberKnife Treatment of Glial Tumors**

**Types of Glial Tumor**

Glial tumors of the central nervous system include astrocytomas, ependymal tumors and primitive neuroectodermal tumors. Of these, astrocytomas are by far the most common and significant. Astrocytomas are graded according to a system devised by the World Health Organization as follows:

Grade 1 astrocytomas are slow-growing, benign, and usually associated with long-term survival. Patients may experience total remission after a complete surgical resection, and even if this is not possible, radiation treatment is usually successful. However, only approximately 2% of astrocytomas are classed as grade 1.

Grade 2 astrocytomas are defined as invasive gliomas, but are relatively slow-growing and usually benign. Unfortunately, over time they may develop into malignant higher-grade tumors. As invasive tumors, complete removal by conventional resection is often impractical, and recurrence is common. Patients are therefore frequently treated with radiotherapy and chemotherapy in addition to surgery. Individuals with grade 2 astrocytomas have a 5-year survival rate of 34% without treatment and approximately 70% with total resection and radiation therapy. Approximately 8% of astrocytomas are classed as grade 2.

Grade 3 astrocytomas are anaplastic astrocytomas. Patients with such tumors often present with seizures, neurological deficits or mental aberrations. Standard treatment has been to remove as much of the tumor as possible without exacerbating the neurological problems. Radiation therapy is a standard component of treatment of grade 3 astrocytomas, and patients so treated have a median survival time of 2-3 years. Approximately 20% of astrocytomas are classed as grade 3.

The grade 4 astrocytoma (also known as glioblastoma multiforme) is the most common and most malignant primary brain tumor, and the second most frequent brain tumor, representing approximately 70% of astrocytomas. The high mortality rates for both grade 3 and 4 astrocytomas partly reflect the fact that the tumors usually remain undetected until they cause neurological symptoms, by which time their infiltrative nature makes complete surgical removal impossible. In the case of grade 4 tumors, therapy has traditionally consisted of attempted gross total resection followed by multifractionated focal EBRT. However, even radical resection combined with radiation rarely eliminates the tumor completely or prevents eventual recurrence, which usually occurs within 2.0 cm of the original tumor margin (22). Records of the Central Brain Tumor Registry of the United States indicate that few patients survive beyond 3 years with a grade 4 glioma: median survival time is 17 weeks without treatment, 30 weeks with conventional radiation treatment, and 37 weeks with surgical removal of most of the tumor followed by radiotherapy. In the prognosis of glioblastoma, age and Karnofsky score are critical determinants, with younger and less affected patients doing far better than elderly incapacitated patients (23), regardless of the treatment options employed.

**Efficacy of CK Treatment of Glial Tumors**

In an early report of CyberKnife treatment of malignant gliomas, Yoshikawa et al. (24) reported their experience with CK treatment of 25 patients with such tumors. For 44 lesions treated (31 glioblastomas, 13 anaplastic astrocytomas), median treatment dose was 20.3 Gy (range: 13.9-26.4). In the 18 glioblastoma patients, median survival after diagnosis was 20.7 months, with a mean follow-up period of 21.5 months, though the interval between diagnosis and CK treatment was variable. Of the 7 anaplastic astrocytoma patients, 6 were
alive with follow-up periods of 11.4 to 52.8 months. Patients younger than 70 years had a median survival after diagnosis of 37.1 months, compared to 12.4 months for older patients. Patients with well-controlled lesions had a median survival after diagnosis of 39.8 months, compared to 16.0 months for those with uncontrolled lesions. Late delayed radiation necrosis was seen in 1 glioblastoma patient, but no other morbidity was observed.

Radiation necrosis is a possible sequel to CyberKnife treatment for any type of tumor, though the incidence seems to be small. In another early study of 61 patients treated with CyberKnife for glioma and glioblastoma using 3-6 fractions, Sato et al. (25) found necrosis in 4 of 61 patients, two of whom required resection to remove the affected tissue. Similar low incidences have been reported by others. However, careful planning and management of the dose can minimize or eliminate this effect. In a study of SRS treatment of recurrent malignant glioma, in which patients were given total doses of 20-50 Gy in fractions of 5 Gy, a total dose of >40 Gy was identified as a major predictor for radiation necrosis (26), but more conservative doses delivered using hypofractionation appear to reduce the occurrence and severity of such necrosis (26, 27). The low recorded incidence of necrosis with CKSRS is in marked contrast to the high incidence commonly seen in glioblastoma patients treated with temporary brachytherapy using implanted iodine-125 seeds after undergoing EBRT (28).

More recently, retrospective studies of the efficacy of CyberKnife in treating both newly diagnosed and recurrent cases of glioblastoma multiforme have been conducted (11, 13), and while the results for treatment of newly diagnosed cases seemed to be promising, a subsequent multi-center study has interpreted the data as indicating that the CyberKnife is best applied to recurrent or progressing glioblastomas rather than upon initial diagnosis.

The first of these studies to be published (11) was a retrospective analysis of 20 glioblastoma multiforme patients who were treated with CyberKnife after gross total resection (n = 11), subtotal resection (n = 8) or biopsy (n = 1). The marginal dose ($D_{90}$) ranged from 19.99 Gy to 41.47 Gy (mean: 34.58 Gy) with a maximum mean dose of 43.99 Gy (range: 23.33-56.89 Gy), delivered in 1-8 fractions. Eight patients also received adjuvant ACNU and Vincristine chemotherapy, but no patient received any other form of radiation therapy in addition to the post-surgical CyberKnife treatment. Overall median survival rate was 16 months, with 55% of patients alive at 12 months and 34% at 24 months. Median survival for patients who received gross total resection was 36 months versus 8 months for those who underwent subtotal resection or biopsy. These results were judged to compare favorably with historic data for patients treated using focal EBRT in newly diagnosed post-surgical glioblastoma patients. These are potentially important results in that, even if the survival advantage following CKSRS is not significantly greater than with focal EBRT, it is surely preferable from the patient’s perspective to receive just a small number of CyberKnife fractions than to have to endure weeks of EBRT sessions only to achieve a similar outcome.

A subsequent multicenter study (13) compared outcomes for 20 patients who underwent CyberKnife treatment at the time of initial diagnosis and/or during the first 3 months of their initial clinical management, and 26 patients who were treated with CyberKnife upon tumors recurrence or progression. In each case, CyberKnife treatment was performed in addition to traditional therapy. Mean survival following diagnosis for the initial treatment group was 11.5 months (range: 2-33 months), compared to 21 months (range: 8-96 months) for patients treated following tumor recurrence or progression. Median survival following CyberKnife treatment was 9.5 months (range: 0.25-31 months) for the newly diagnosed patients and 7 months (range: 1-34 months) for the patients with recurrent tumors. Statistical analysis shows that survival time did not correlate with treatment parameters or target volume; patients who underwent more extensive surgical interventions survived longer, especially if total tumor resection was performed. The authors conclude from their data that there is, in fact, no apparent survival advantage to using CK in the initial management of glioblastoma patients, and that it should be reserved for patients whose tumors recur or progress after conventional therapy.

There is growing evidence that gross total resection of glioblastoma improves outcome, regardless of additional treatments (29, 30). Accordingly, Stummer et al. evaluated the use of 5-aminolevulinic acid (ALA) to improve the incidence of complete resection (31, 32) and obtained markedly improved outcomes. However, the infiltrative nature of glioblastoma multiforme implies that any residual tumor will be in the boundary of the tumor as seen on FLAIR MRI (as opposed to the contrast-enhancing portion of the tumor), in which case CKSRS of this infiltrative penumbra might improve outcome as compared to resection or even resection in combination with external beam radiation therapy, since the superior conformality and precision obtainable with the CyberKnife beam minimizes the risk of inducing the neurological deficits associated with WBRT.

A further possible improvement would be the use of radiosensitizing agents which increase the sensitivity of tumor cells to radiation. Some of these have already been found to enhance the effectiveness of conventional radiotherapy for gliomas (33), and there are preliminary indications that administration
of Temozolomide in combination with CKSRS may improve the outcome in patients with recurrent high-grade gliomas (34), but no peer-reviewed studies confirming this have yet been published.

CyberKnife Treatment of Metastatic Brain Tumors

Brain metastases occur in 5-10% of all adult cancer patients and affect nearly 170,000 individuals in the US each year. The most common primary source of brain metastases is lung cancer, followed by breast cancer, and then unknown primary tumors and melanoma (35). In contrast, primary brain tumors are far less common than metastases from elsewhere, with an estimated incidence of approximately 39,000 per year in the US (36).

The high rates of recurrence following resection of brain metastases have resulted in radiotherapy being used in conjunction with surgical resection. CyberKnife radiosurgery may achieve comparable results to surgical resection for a single metastasis, and offers a superior option in cases involving multiple metastases, since the lesions can more easily be treated in the same session.

In an early study by Shimamoto et al. (37), 66 metastases in 41 patients were treated with the CyberKnife, using a prescribed dose of 9 to 30 Gy delivered in a single fraction, with a D90 of 10.5 to 33.7 Gy. It was found that freedom from progression (FFP) during the follow-up period was more likely with a prescribed dose of at least 24 Gy (6-month FFP = 80%) than with a dose of ≤ 20 Gy (6-month FFP = 44%). Of the 36 patients who had received no WBRT before or current with the CyberKnife treatment, 13 developed new intracranial lesions during the follow-up period. No new lesions were observed in the other 23 patients, but their median overall survival was only 3.5 months, meaning that they died before new lesions were detected. The median time between CyberKnife treatment and detection of new intracranial lesions was 8.3 months (range 2.0-14.0 months).

Nishizaki et al. (38) reported results for 71 patients with 148 metastatic brain lesions. Forty patients had a single lesion, and 31 had multiple lesions. Mean marginal dose was 20.2 Gy, delivered in 1-3 fractions. Overall 6-month and 1-year survival rates were 74% and 47%, respectively, with a median survival time of 56 weeks. Age or presence of multiple metastases did not influence prognosis. Twenty-five patients developed 92 new metastases outside the treated lesions, and of these, 21 patients (84 lesions) received salvage CyberKnife treatment.

More recently, Hara et al. (39) examined 62 patients with a combined total of 145 brain metastases of either renal cell carcinoma (18 patients) or malignant melanoma (44 patients) who underwent CKSRS. The mean prescribed dose was 20 Gy, and the mean survival after CK treatment was 8.3 months. One-year intracranial progression-free survival was 38% and incidence of local control was 87%. Interestingly, while intracranial control was found to be improved by previous whole-brain radiotherapy or chemotherapy, surgical resection had no effect on intracranial or local control. Melanoma was associated with decreased intracranial control. Incidence of radiation necrosis in this study was 6%.

Wang et al. (40) used fractionated dose CKSRS to treat 40 patients with a total of 68 brain metastases. The primary lesions from which these metastases derived comprised 26 lung cancers (20 squamous cell carcinomas and 6 adenocarcinomas), 4 breast cancers (all invasive ductal carcinomas), 4 digestive cancers (2 squamous cell carcinomas and 2 adenocarcinomas), 1 renal cancer (a clear cell carcinoma), and 4 unclear primary lesions (1 squamous cell carcinoma and 3 adenocarcinomas). Total hypofractionated doses of 18-36 Gy (5-25 Gy/fraction; 1-5 fractions) were employed, and the patients were followed for over 14 months post-treatment. After 3 months, the local control rate and therapeutic effective rate for metastatic tumors were 77.9% and 94.1%, respectively. The 3-month, 6-month and one-year patient survival rates were 97.5%, 82.5% and 67.5%, respectively.

One group evaluated the CyberKnife in comparison to the GammaKnife using matched-pair analyses and found that the different treatment parameters associated with the two systems apparently have no significant impact on the quality of clinical outcome for patients with single brain metastases (41). The only significant difference between the two treatment groups was that CyberKnife-treated patients survived twice as long as GammaKnife-treated patients, and while this is clearly a desirable result, the authors suggest that it could simply reflect the more intensive approach to anticancer therapy that has been prevalent in recent years while CyberKnife has been available. (The patient group comprised 423 GammaKnife patients and only 73 CyberKnife patients, from which 63 good matches were obtained. It is noted that dose-related parameters were significantly higher in the GammaKnife group.)

Most published studies of CyberKnife treatment of brain metastases have included tumors at various locations within the brain. However, Cheshire et al. (42) have evaluated the effectiveness of CyberKnife in the treatment of lesions specifically located in the foramen magnum. Of the 35 patients treated, 25 had benign tumors (9 meningiomas, 5 schwannomas, 4 neurofibromas, 3 hemangiblastomas, 2 ependymomas, 1 chordoma and one pilocytic astrocytoma) and 10 had malignant growths (9 metastases and 1 chondrosarcoma).
specific fractionation schedule (mean: 1.8 sessions; range: 1-5) was based on the size of the lesion, and the mean dose was 19 Gy. In the 23 patients for whom radiographic follow-up was obtained, 9 lesions (39%) were stable, 10 lesions (43%) decreased in size and 4 lesions (17%) increased in size. In terms of symptom relief, 11 (46%) of 24 patients experienced no change, 7 (29%) experienced improvement, and 6 (25%) experienced deterioration. There were 11 deaths in the series, 8 related to the disease and three from unrelated causes. Complications related to the CyberKnife treatment were noted in 4 (11%) of the 35 patients, specifically one case of temporary emesis immediately after treatment, one case of cystic enlargement at 2 months, and two cases of radiation necrosis (at 1.5 and 2.5 years post-treatment). While outcomes varied significantly, as would be expected with such a mixed group of tumors, it is noted that the use of CyberKnife to treat such lesions greatly reduces the risk of damage to the lower cranial nerves, which has been long associated with conventional surgical interventions in this anatomical region.

Case Study – Metastatic Melanoma

The complexity associated with the management of patients with rapidly progressive metastatic disease can be best illustrated in a case currently under management at our medical center. The patient is a 40-year-old white female diagnosed with melanoma with biopsy of a left thigh lesion 4 years ago, initially managed by wide excision of the area and sentinel lymph node biopsy which was negative for involvement. No adjunct treatment was given. Two years later, multiple thigh lesions were removed and demonstrated recurrent melanoma, with repeat groin resection yielding multiple lymph nodes which were negative for involvement. Nine months later, a mass in the right abdomen was removed and shown to be metastatic melanoma (4/2009), along with a mass

Figure 1: Right superior medial parietal lesion 3 weeks prior to radiosurgery (A), immediately prior to radiosurgery (B) and 1 month after CKSRS (C). In the 3 weeks prior to radiosurgery, the length of the long axis indicated in (A) increased rapidly from 26.7 mm to 37.0 mm (a 39% increase in that dimension alone), but CKSRS (2700 cGY, 80% isodose, 2 fractions) halted this growth.
in the left upper lobe of lung. The patient was given four cycles of chemotherapy consisting of Temodar, Vinblastine, Cisplatin, Interleukin and Interferon, followed by 4 cycles of maintenance chemotherapy completing 5 months from initial biopsy (approximately 9 months ago). The lung mass progressed in size, and wedge excision was performed 6 months ago with pathology showing metastatic melanoma. An MRI of the brain demonstrated a lesion in the left parietal lobe, two in the right parietal lobe (Figure 1A), and one in the cerebellar hemisphere (Figure 2A). Neurologically the patient was intact.

Cyberknife SRS was performed on the left parietal (2400 cGy to the 80% isodose) and the superficial right parietal mass (2100 cGy to the 77% isodose). Prior to treatment of her cerebellar lesion the patient experienced nausea and vomiting with a seizure. A CT scan demonstrated hemorrhage into the (treated) left parietal lesion and the (untreated) cerebellar lesion. The patient was placed on anticonvulsants and dexamethasone with neurological improvement.

Following titration of her steroids the patient deteriorated and experienced recurrent nausea and vomiting. In spite of her steroids being increased, she presented 2 weeks later with left arm weakness and recurrent seizures; a CT scan demonstrated hemorrhage in the left superficial lesion and increased edema around and enlargement of the cerebellar lesion with increased mass effect and effacement of the fourth ventricle. The cerebellar lesion was stereotactically resected via a left retrosigmoid approach (Figures 2B and 2C) with pathology confirming metastatic melanoma. Her postoperative course was complicated with a pulmonary embolism treated through placement of an inferior vena caval filter, as anticoagulants were felt to be contra-indicated due to prior cranial hemorrhage. Clinically the patient improved following surgery; however, the right superior medial parietal lobe lesion was observed to be growing rapidly: in just three weeks its long axis increased from 26.7 mm to 37.0 mm, representing a 39% increase in that dimension alone, and a volumetric increase of approximately 250% (compare Figures 1A and 1B). The lesion was treated with CKSRS

![Figure 2: Cerebellar lesion before surgery (A), immediately following surgery (B) and approximately 2 months post-surgery (C).](image-url)
consisting of 2700 cGy to the 80% isodose line in 2 fractions and no further growth of this tumor occurred (Figure 1C). The patient did well until one month later, when once again she experienced headache with nausea and vomiting. A CT scan demonstrated some reduction in size of the right parietal lesion, but an increase in vasogenic edema surrounding it and massive return and regrowth of her cerebellar lesion. Steroids were restarted and the patient has been continued on Temodar, IL-2 and Avastin. CyberKnife SRS is planned for the cerebellar lesion as salvage therapy.

This patient demonstrates the complexity of a rapidly growing tumor with an inherent propensity to hemorrhage and spread to multiple areas causing a variety of symptoms that are treated with a combination of stereotactic surgery, radiosurgery, and chemotherapy. Although in this case care was only palliative, it can be concluded that this intensive management resulted in prolongation of high-quality life with essentially no permanent neurological deficit.

Conclusions

The use of CyberKnife SRS in the management of brain tumors is still very much in its infancy. Key parameters such as dose, number of fractions, technique of defining the target volume, use as primary therapy versus as an adjuvant, and the effect of tumor type have not been studied even in a careful retrospective fashion, much less as a randomized prospective manner which could yield class I data. Given the paucity of reports of the use of CKSRS in this context, it is impossible to make a conclusion as to the proper applications of this exciting technology. As the use of CKSRS has been the most intense in tumors of the cerebellopontine angle, it appears clear that at the very least CKSRS yields results equivalent to those achieved with frame-based SRS, and may actually be better, given the ability to hypofractionate with the frameless technique which may reduce the incidence of cranial nerve deficit. As the complication rate for either form of SRS appears to be lower than that associated with surgical resection (43), it could be argued that the initial treatment of these lesions upon presentation should be radiosurgical as opposed to surgical. Surgery in these cases would therefore be relegated to lesions recurring after SRS, or in patients who are either very young (making long-term control an important consideration) or have very large tumors in which the radiation dose must be lowered dramatically to reduce the risk of radiation necrosis.

For metastatic tumors the use of CKSRS would appear to be ideal, as management of these tumors in single or a few fractions with control comparable to surgery or external beam irradiation would afford patients significant improvement in their quality of life. Furthermore, avoidance of cognitive impairment caused by irradiation of normal brain tissue could also have a dramatic impact on quality of life in these patients with limited life expectancy.

Finally, the use of CKSRS in malignant glial neoplasms remains highly controversial. It is clear that the goal of treatment upon initial presentation should be gross total resection of the contrast-enhancing portion of the tumor as afforded by surgical resection. However, there is no question that adjuvant therapy such as chemotherapy (44) or through the use of radiation is important in maximizing time to recurrence of these rapidly growing lesions. Given the recent success of chemotherapy including angiogenesis inhibitors such as Avastin (bevacizumab), it would seem unlikely that CKSRS will replace chemotherapy for these lesions. Rather, it would appear that CKSRS will assume a “third line” role in the management of these difficult lesions, being relegated to the treatment of recurrent lesions that have proven to be resistant to surgery and chemotherapy.

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