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Original papers

Frame-based and frameless stereotactic radiosurgery for intracranial and extracranial tumors

Zbigniew Petrovich, Cheng Yu

Purpose. During the past 10 years stereotactic frame-based radiosurgery (SRS) emerged as an important treatment modality in the management of selected intracranial lesions. More recently, frameless SRS has extended the potential of ibis treatment to include lesions virtually in any site of the body.
Patients and methods. Many thousands of patients are being treated annually with frame-based SRS limited to the cranial cavity. A total of 180,222 patients were treated to December 2001 with gamma knife (GK) and, very likely, a similar number was treated with various linear accelerator based SRS systems. Frameless SRS has been performed uncommonly until cyber knife (CK) became available. Over 3,000 patients were treated with CK in the US and Japan. This included patients treated for extracranial lesions. Treatment results in patients treated with GK at University of Southern California (USC) will be presented.
Results. From 1994 to 2002, a total of 1,126 patients received GK at USC for various indications. Since metastatic tumor constituted the largest (42.4%) diagnostic category treated, the outcome in this group is specifically discussed. The overall median survival was 9.2 months. The median survival was 8.3, 9.0, 17 and 12 months, for melanoma, lung cancer, breast cancer and renal cell carcinoma, respectively. In multivariate analysis Karnofsky's performance status (70 vs. >70), status of systemic disease (inactive vs. active), tumor histology and total intracranial tumor volume were the only important factors predictive of survival, p=0.0001. Cause of death was found to be due to CNS problems in about 25% of patients with a diagnosis other than melanoma, while it was 42% in those with melanoma. GK SRS was given on an outpatient basis and was very well tolerated by the patients. Symptomatic focal radionecrosis requiring craniotomy for its removal was noted in <5% of patients.
Conclusions. An excellent palliative benefit was obtained in nearly all patients. The treatment was compatible with a good quality of life.

Radioterapia stereotaktyczna, z unieruchomieniem lub bez, w leczeniu guzów śród- i pozaczaszkowych

Cel. W ciągu ostatnich 10 lat radioterapia stereotaktyczna stała się wiodącą metodą terapii wybranych zmian wewnątrzczaszkowych. Ostatnio wskazania do radioterapii stereotaktycznej znacznie się poszerzyły, obejmując zmiany praktycznie w dowolnej lokalizacji, co wiąże się z możliwością zrezygnowania ze stosowania unieruchomienia dzięki postępom technik wizualizacji.
Materiał i metody. Co roku wiele tysięcy chorych poddawanych jest leczeniu zmian wewnątrzczaszkowych techniką radioterapii stereotaktycznej. Do grudnia 2001 r. metodę tak zwanego gamma-noża (Gamma-knife) zastosowano u 180 222 chorych i, prawdopodobnie, u porównywalnej grupy chorych wykorzystano różne inne systemy radioterapii stereotaktycznej, z zastosowaniem akceleratorów liniowych. Radioterapia stereotaktyczna bez unieruchomienia stosowana była rzadko, dopóki nie wprowadzono do użycia tzw. cyber-noża (Cyber-knife - CK). Na terenie Stanów Zjednoczonych i w Japonii technikę CK zastosowano dotychczas u około 3000 chorych, w tym również z guzami pozaczaszkowymi. W pracy przedstawiono doświadczenia University of Southern California w zakresie leczenia chorych z zastosowaniem GK.
Wyniki. W latach 1994-2001 technikę GK zastosowano, z różnych wskazań, u 1126 chorych. Najczęściej leczono guzy przerzutowe (42,4% chorych), a zatem ta grupa chorych została najszerzej omówiona. Całkowita mediana przeżycia wyniosła 9,2 miesiąca - odpowiednio 8,3; 9,0; 17 i 12 miesięcy dla chorych z czerniakiem, rakiem płuca, rakiem piersi i rakiem nerki. Po zastosowaniu analizy wielowariantowej wykazano, że jedynymi czynnikami istotnymi dla przeżycia były: ocena stanu ogólnego wg skali Karnofsky'ego (70 vs.>70), stadium choroby systemowej (nieaktywna vs. aktywna), typ histologiczny

Department of Radiation Oncology,
University of Southern California School of Medicine,
Los Angeles, California, USA

guza oraz całkowita śródczaszkowa masa nowotworu (p=0,0001). Zmiany w ośrodkowym układzie nerwowym były przyczyną zgonu u ok. 25% chorych z rozpoznaniem innym niż czerniak i u ok. 42% chorych z czerniakiem. Radioterapia stereotaktyczna z użyciem GK była stosowana w trybie ambulatoryjnym i była bardzo dobrze tolerowana przez chorych. Objawowa ogniskowo występująca martwica tkanek, spowodowana radioterapią, wymagała interwencji neurochirurgicznej u mniej niż 5% chorych. Wnioski. U niemal wszystkich chorych obserwowano znakomite wyniki leczenia paliatywnego. Postępowanie zapewniało dobrą jakość życia.

Key words: Frame-based, frameless stereotactic radiosurgery
Słowa kluczowe: radioterapia stereotaktyczna (z unieruchomieniem, bez unieruchomienia)

Introduction

In the last two decades of the 20th century there bas been an unprecedented growth of computer technology, which propelled the development of progressively more sophisticated, imaging techniques. This was particularly true in the case of computerized axial tomography (CT) and magnetic resonance imaging (MRI). In this environment of technological innovations there has been an increasing interest in stereotactic radiosurgery (SRS). The wide use of SRS helped to redefine the management of patients with virtually all benign and malignant brain lesions and selected functional disorders [1]. SRS typically uses various energy static or dynamic (multiple arcs) photon beams and, less frequently, proton beams. The main difference between the conventional external beam radiotherapy and SRS is the ability of the latter to precisely deliver a high dose of radiation to a well-defined and relatively small target volume usually using a single radiation fraction. There is a sharp radiation dose fall off outside of the target volume thus optimizing protection of the normal brain tissue.

In the late 1960's gamma knife (GK) SRS was introduced to the clinic by a Swedish neurosurgeon Dr. Lars Laksell. The current GK models use 201 fixed Cobalt-60 beams. In the early 1980's, in Europe and later in the US there was a development of linear accelerator-based SRS systems. The present day systems most frequently use 4-6 MV photon beams. Both GK and accelerator based systems require a rigid immobilization with the use of various design head frames. This requirement makes the treatment somewhat uncomfortable to the patient and multi-fraction SRS becomes impractical.

In the early 1990's a dedicated frameless SRS system, called cyber knife (CK) was developed by a Stanford University neurosurgeon Dr. John Adler [2-5]. CK uses a specially designed and light weight 6 MV, linear accelerator, which is attached to a robotic arm and it contains a sophisticated imaging system allowing for a real time verification of the targeting accuracy.

The development of CK was a major event in SRS for the following reasons: 1. It made rigid head frames to a large extent obsolete thus improving the treatment tolerance; 2. It permitted for an easy use of multifraction SRS; and 3. It most importantly extended the application of SRS to any part of the human anatomy. It is apparent that this new SRS system will find a very important place in the management of patients with benign and malignant primary and metastatic tumors. Wide application of CK is likely to result in an improvement of the quality of life of oncological patients. CK frameless system clearly represents a new important dimension in the field of radiosurgery and the very future of SRS.

Gamma Knife SRS

GK SRS is a commonly applied treatment for a wide spectrum of intracranial lesions or functional disorders. The interest in this treatment has been increasing over the past decade. At the present time there are over 170 GK facilities worldwide. A total of over 180,000 patients were treated worldwide to December 31, 2001 (Table I). Most (51%) patients were treated in Asia, with the US contributing 28% to the total and Europe 20%. In the early days of GK SRS functional disorders, vascular lesions and benign tumors were primarily treated. At this time malignant tumors represent 40.4% of all GK treatments, with metastatic lesions being clearly the

Table. I. Malignant and benign tumors treated with gamma knife word-wide to December 31.2001*

Tumor	N	%
Malignant		
Metastasis	53,011	72.9
Gliomas	14,778	20.3
Nasopharyngeal ca	828	1.1
Uveal melanoma	705	1.0
Glomus tumor	515	0.7
Hamangiopericytoma	511	0.7
Chondrosarcoma	190	0.3
Other malignant tumors	2,171	2.9
TOTAL	72,709	100.0
Benign		
Meningioma	22,529	34.8
Acoustic neuroma	17,154	26.5
Pituitary adenoma	15,816	24.4
Craniopharyngioma	1,955	3.0
Pineal tumor	1,941	3.0
Trigeminal neuroma	1,118	1.7
Schwannoma	1,041	1.6
Chordoma	930	1.4
Hemangioblastoma	883	1.3
Other benign tumors	1,355	2.1
TOTAL	64,722	100.0
TOTAL all tumors	137,431	76.2

* Courtesy of Leksell Gamma Knife Society

number one indication for this therapy (Table I). Among benign tumors the most common indication for GK is meningioma followed by acoustic neuroma and pituitary adenoma. A particularly useful indication for GK SRS is represented by tumors located in the cavernous sinus where SRS obtained results have been excellent [6]. Similarly, treatment outcomes in patients with recurrent or persistent pituitary adenomas following transsphenoidal resection have also been excellent [7-10]. An important and growing indication for GK SRS is acoustic neuroma where there is reported a high incidence of tumor control rates and a good preservation of hearing. Illustrations of treatment plans for various benign tumors including chordoma, meningioma and pituitary adenoma, obtained with model C, GK SRS at USC are shown in Figure 1 through 4. All four tumors were successfully treated with a good protection from therapeutic doses of radiation of the adjacent important and radiosensitive normal structures. The use of small (8 mm) collimators and multiple isocenters facilitated development of good conformal treatment plans, which were critically important in meeting the above defined goals.

Vascular lesions (primarily arteriovenous malformations) remain an important indication for GK representing over 17% of all patients treated with this modality (Table II). In the group of functional disorders, trigeminal neuralgia represents the most frequently used and important indication for GK (Table II). Treatment for epilepsy and Parkinson' s disease intractable to medical therapy are relatively new indications for GK, which are currently being investigated. A caution needs to be exercised with the use of SRS for functional disorders, since treatment outcomes in this group of diseases is frequently not well defined and it is difficult to objectively measure.

Table II. Vascular lesions and functional disorders treated with gamma knife world-wide to December 31,2001*

Vascular	N	%
AVM	28,925	93.7
Aneurysm	112	0.4
Other vascular	1,828	5.9
TOTAL	30,865	100.0
Functional Disorders		
Trigeminal neuralgia	8,761	73.5
Epilepsy	1,320	11.1
Parkinson's disease	988	8.3
Intracable pain	346	2.9
Psychoneurosis	103	0.9
Other	408	3.4
TOTAL	11,926	100.0
TOTAL vascular& functional disorders	42,791	23.7

* Courtesy of Leksell Gamma Knife Society

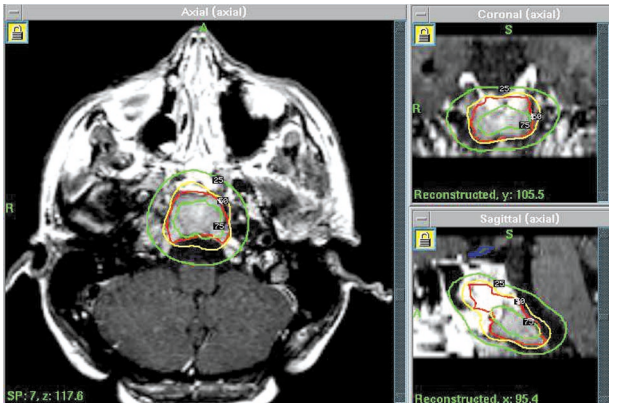

Figure 1a

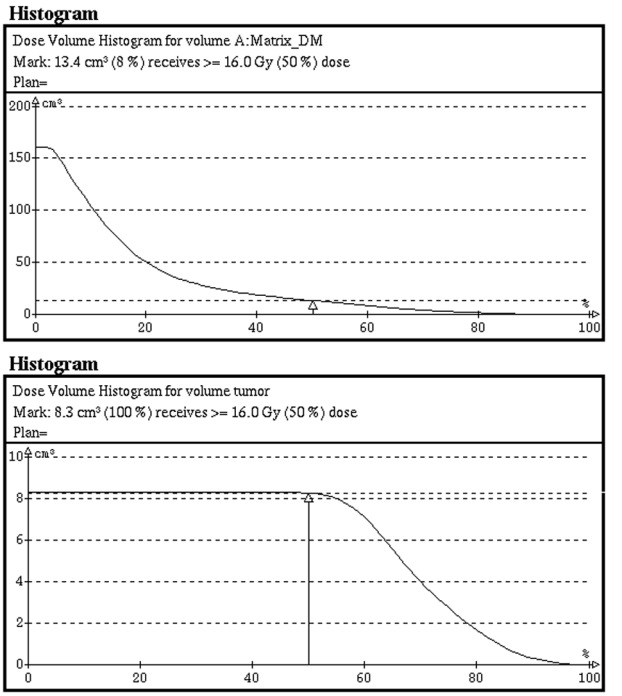

Figure 1b

Figure 1

1a. This is a case of a 16-year old female patient who was diagnosed with a large clival chordoma. She underwent transsphenoidal surgery with subtotal resection for a 2.3x2.4x2.4 cm tumor of the c1ivus displacing the basilar arteries and involving the posterior part of the sphenoid sinus. Residual tumor was noted together with microscopic evidence of sphenoid sinus involvement. About 7 months following surgery she presented for GK SRS. On MRI obtained for the GK treatment planning a 2.7x2.3x2.7 cm mass was noted. The patient was treated to 16 Gy defined to the 50% isodose line with the use of 8 mm collimators and 8 isocenters. Total tumor volume was 8,3 cm^3 and total volume treated was 13.4 cm^3 with 100% of the tumor included in the 50% isodose line. Excellent conformal treatment plan was obtained and it is demonstrated on axial coronal and sagittal MRI views. A good treatment tolerance was noted with no change in the tumor appearance and dimensions during 1 year of observation.

1b. Dose volume histogram is provided for this patient.

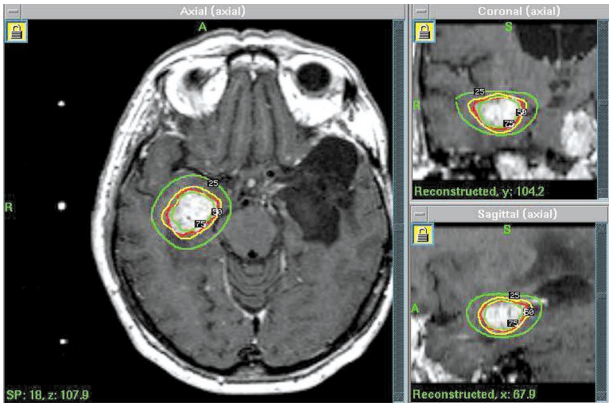

Figure 2a

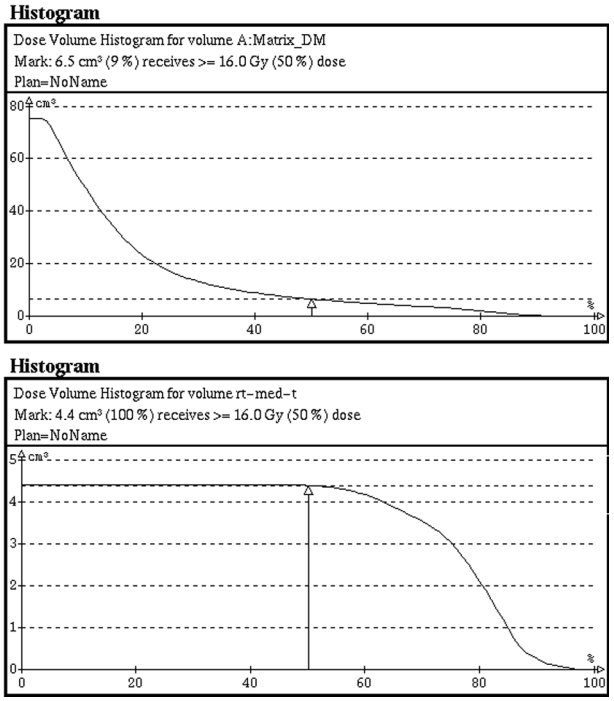

Figure 2b

Figure 2

2a. The patient is a 60-year old female diagnosed 6 years before with a large left parasellar mass. She was treated with a craniotomy and total gross tumor removal. Histological diagnosis was that of meningioma. At this time patient presented with a right medial temporal lobe meningioma measuring 2.5x3.5x1.6 cm. The patient was treated with GK SRS receiving 16 Gy to the 50% isodose line with 5 isocenters. Tumor vo1ume was 4.4 cm^3 and the treated volume was 6.5 cm^3 with 100% of the tumor encompassed by the 50% isodose line. Special care was taken to protect the adjacent pons from high radiation dose.

2b. Dose volume histogram.

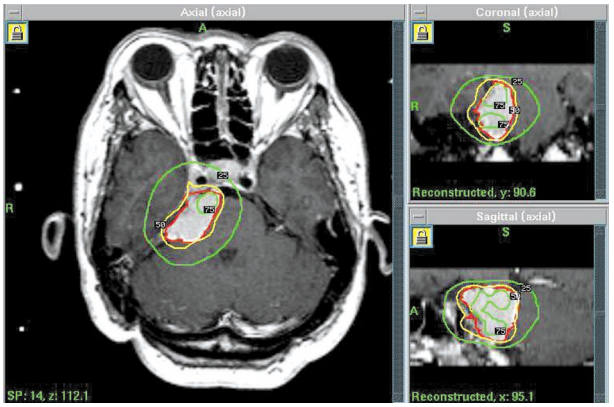

Figure 3a

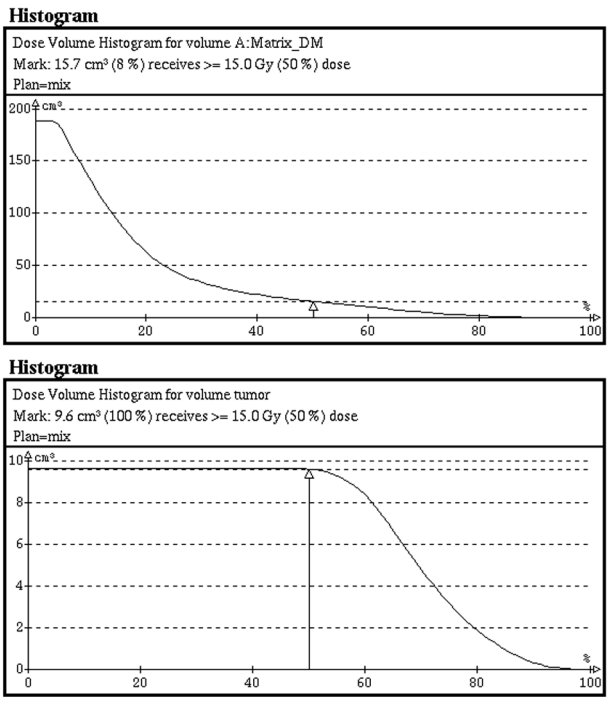

Figure 3b

Figure 3

3a. This patient is a 67-year old female who presented with nausea, vomiting and ataxia. She was diagnosed with peripontine meningioma. Her tumor likely originated in petroclinoid area extending into the Meckel's cave and the posterior part of the right cavernous sinus and an obvious encroachment on the adjacent pons. The lesion measured 30x35x32 mm. GK SRS was felt to be the only available effective treatment for this patient. She received 15 Gy to the 50% isodose line using 11 isocenters with 8mm collimators. A good conformal treatment plan was developed with 100% of the tumor being treated. Please note the 50% isodose line being close to the tumor minimizing radiation exposure to the pons.

3b. Dose volume histogram.

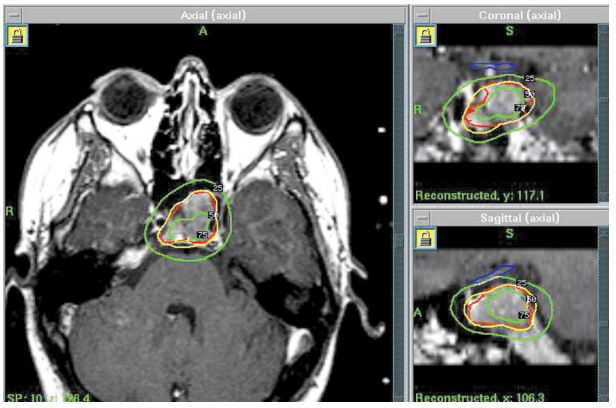

Figure 4a

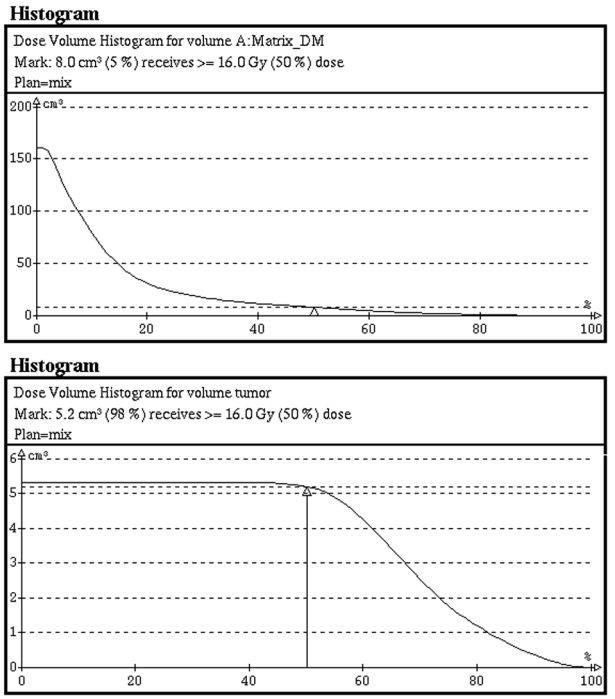

Figure 4b

Figure 4
4a. A 19-year old male patient was originally diagnosed 26 months ago with prolactin- secreting pituitary adenoma. The treatment consisted with a transsphenoidal procedure with a steep fall in the serum prolactin level. Prolactin level, however, began to increase and the patient was diagnosed with a recurrent tumor in the left cavernous sinus. The tumor measured 28x25x20 mm. In order to keep the radiation dose to the left optic nerve to < 8 Gy a total of 16 Gy instead of the planned 18 Gy was given using 9 isocenters with 8 mm collimators. A total tumor volume was 5.2 cm³ with 100% of this volume being treated. Please note a very good conformal treatment plan shown in axial, coronal and sagittal views. There was no treatment related toxicity.
4b. Dose volume histogram.

Linear Accelerator Based SRS Systems

It is believed that this form of SRS is as frequently applied as GK. Radiation dosimetry in most cases is about equivalent to that of GK. In recent years, dedicated SRS systems have become widely available making this treatment modality more attractive than in the past. The main problem, however, is a difficulty in obtaining reliable data from many hundreds of medical centers worldwide which operate such linac-based SRS systems. The reported treatment results have be en excellent and equal to the best outcomes obtained with GK [11-14].

Frameless SRS

As it has already been stated, frameless stereotactic systems are more appealing since they provide a better alternative to the more invasive head frames. Patients can be treated most of the time in greater comfort without the need for local anesthesia or systemic sedation. The use of more than one fraction treatment course is readily available. There is also a major advantage in its ability to treat intracranial as well as all extracranial targets. Preliminary data on the experience with frameless stereotactic radiotherapy was reported from University of Florida at Gainesville, Florida [15]. Apparently, treatment reproducibility was reported to be excellent with very small translational and rotational errors.

The full stereotactic potential, however, was realized with the introduction of CK [2-5]. This innovative instrument utilizes a lightweight 6 MV linear accelerator operated with a computer controlled robotic arm and real time image verification of a treated target [3]. CK is being phased in a growing number of medical centers in the US and Japan.

This instrument was recently installed also at USC. The increased availability of CK in turn helps to study the treatment efficacy in various intracranial and extracranial lesions, thus allows for a relatively rapid expansion of the indications for stereotactic radiosurgery [16-19]. Carefully selected spinal tumors and vascular malformations are particularly appealing indications for CK [17-19]. The procedure is performed on an outpatient basis without the need for anesthesia or rigid, bone-anchored fixation. The treatment accuracy has been excellent with dose delivery within a mean of 1.5 mm of the intended target [17]. Patient movement during the treatment delivery was insignificant with a mean of 0.5 mm. Typically, a single, large radiation fraction is used for the treatment with same patients being considered for two or more fractions [17, 19]. CK boost dose to augment external beam radiotherapy for carcinoma of the nasopharynx bas been found to be effective in reducing radiotherapy toxicity and increasing tumor response rates as compared to those obtained with the conventional radiotherapy alone [16]. Indications for CK either well established or under study include the following: 1. Selected intracranial benign and malignant tumors; 2. Intracranial and spinal AVM; 3. Intracranial

functional disorders such as trigeminal neuralgia; 4. Selected benign and malignant spinal tumors; 5. Primary or recurrent tumors of the upper aero-digestive passages; 6. Solitary primary or metastatic lung cancer; 7. Carcinoma of the pancreas; 8. Selected liver metastasis; 9. Adrenal metastasis; 10. Selected patients with renal cell carcinoma; and 11. Adenocarcinoma of the prostate. Many other indications for CK are currently being considered for clinical studies.

USC Stereotactic Program

Over the past 25 years USC has developed a strong interest in the SRS program (Table III). This was initiated in 1980 with stereotactic brachytherapy using Ir-192. Following the ana1ysis of treatment outcomes in this group of patients, no significant improvement in survival or quality of life was detected. There was also a relatively high cost to this program as well as treatment toxicity. Based on the above findings, the stereotactic brachytherapy program was phased out at USC in the late 1980s [20]. A linear accelerator based SRS system was developed at USC in 1985, initially for intracranial targets and in 1995 it was expanded to include selected extracranial sites. In 1994, our SRS program was further augmented with a gamma knife model U, which in 2000 was replaced with model C. In 2002, we acquired a cyber knife. Due to the availability of all basic stereotactic instruments at USC, we have a true privilege of being able to select an optimal treatment mode for a given clinical problem [21]. During the past 20 years we developed a well-functioning, multidisciplinary radiosurgery team (Table IV). Based on our experience we believe that the presence of such a team in a medical center constitutes a basic requirement prior to considering treatment of patients with SRS.

Table III. USC stereotactic program

Year began	Treatment mode
1980	Streotactic brachytherapy Ir-192
1985	Linac-based SRS - 4 MV photon beam
1994	Gamma Knife Model U-Co-60
1995	Linac-based Extracranial SRS-6-20 MV photon beams
2000	Gamma Knife Model C - Co-60
2002	Cyber Knife - 6 MV photon beam

Table IV. Radiosurgery Team

Radiosurgery Team
Neurosurgeon
Other surgical specialties:*
General surgery
Head & Neck surgery
Thoracic surgery
Urology
Radiation Oncologist
Radiation Physicist
Diagnostic Radiologist
Anesthesiologist
Pathologist
Technician
Nurse

* This applies to patients with extracranial sites

Materials and methods

A total of 1,126 patients were treated with GK at USC between 1994 and 2002. They received 1,411 separate treatment sessions for the management of 2,132 lesions (Table V). Metastatic lesions were treated in 42.4%, meningioma in 15.3% and malignant glioma in 9.4% patients. Other diagnoses were less commonly treated (Table V). Of the 477 patients presenting with brain metastatic disease, there were the following primary sites: cutaneous melanoma in 241 (50.5%), lung in 97 (20.3%) and breast, RCC and tumors of other sites being next in frequency (Table VI). Nearly 60% of patients presented with a solitary metastasis, 25% had 2 lesions and 20% had 3 or more lesions. None of the patients was treated for 6 or more metastatic tumors. Median tumor volume was 0.9 cm^3 with a range from 0.1 to 40.3 cm^3. All patients had histological confirmation of a diagnosis of cancer at a primary site. Histological confirmation of brain metastasis was available in

Table V. Indications for gamma knife at USC

Diagnosis	N Patients	%	N Treatments	%	Lesions	%
Metastasis	477	42.4	716	50.7	1,370	64.3
Melanoma	241	50.5	368	51.4	752	54.9
Lung ca	97	20.3	150	20.9	280	20.4
Breast ca	41	8.6	67	9.4	115	8.4
Renal cell ca	32	6.7	48	6.7	78	5.7
Colon ca	16	3.3	21	2.9	37	2.7
Other sites	50	10.5	62	8.7	108	7.9
Meningioma	172	15.3	188	13.3	208	9.8
Malignant glioma	106	9.4	113	8.0	117	5.5
Pituitary adenoma	86	7.6	82	5.8	93	4.4
AVM	78	6.9	79	5.6	81	3.8
Trigeminal neuralgia	71	6.3	75	5.3	75	3.5
Acoustic neuroma	35	3.1	39	2.8	39	1.8
Other lesions	101	9.0	119	8.4	149	7.0
Total	1,126	100.0	1,411	100.0	2,132	100.0

Table VI. Survival in patients with brain metastasis at USC

Primary site	N	%	Median survival (months)
Melanoma	241	50.5	8.3
Lung	97	20.3	9.0
Breast	41	8.6	17.0
Kidney (RCC)*	32	6.7	12.0
Other	66	13.8	5.8
TOTAL	477	13.8	9.2

* Renal cell carcinoma

patients who had a prior craniotomy or required a stereotactic biopsy if a diagnosis of metastatic disease was questionable. An overwhelming majority of the study patients, however, had their diagnosis of brain metastasis based on MRI findings.

Most of the treated patients were referred from the outside of this medical center and were presenting to us with already completed diagnostic systemic work up. There was a slight (male 52% vs. female 48%) male preponderance. Patient age ranged from 21 to 90 years with a median age of 57 years. Patients were considered for GK SRS if they met the following criteria: 1. Stable general condition; 2. Expected survival >3 months; 3. Solitary or < 6 lesions, in patients with prior whole brain irradiation and recurrent tumor and up to 4 lesions in the previously untreated patients; 4. The largest tumor diameter was not to exceed 35 mm; 5. No acute signs and symptoms of increased intracranial pressure. Patients with these signs were considered for a conventional craniotomy. Important details on patient work up and the treatment protocol have been presented elsewhere [1, 9, 22-26]. A majority (57%) of patients presented with active systemic disease while the remaining patients had stable or inactive systemic disease. Prior to or subsequent to GK SRS, whole brain irradiation (WBI) was given to 114 (24%) patients. This treatment consisted of 30 Gy given in 2 weeks or 40 Gy in 4 weeks. Most of the treatment decisions regarding WBI were made and the treatment itself was given in outside medical centers. Nearly twice as many patients received WBI prior to GK SRS while a minority received this treatment following GK. Based on our review it was difficult to establish a uniform pattern for indications for WBI. Same patients received WBI for a single metastatic lesion while others had a few to several lesions. All patients referred for GK following WBI had evidence of intracranial tumor progression.

Radiation dose was determined based on a number of parameters such as tumor volume, tumor histology and tumor location in the brain. Basically, patients with a diagnosis of melanoma, RCC or sarcoma were given a dose of 20-22 Gy while patients with breast carcinoma or lung cancer were given 18-20 Gy. Median radiation dose for all patients was 20 Gy usually defined to the 50% isodose line. Patients who were treated following WBI received 16-18 Gy. Those patients with tumors >9 cm^3 received a 10% lower radiation dose than expected from their histological diagnosis. Anti-seizure medications were given prophylactically to patients with cortical lesions usually for a period of 2 weeks following GK. Dexamethason was given only to patients with symptoms and signs of increased intracranial pressure or to those with larger (>20 cm^3) tumors. Survival was calculated in months from the date of GK SRS. Informed consent was obtained in writing from all patients. Patients had regular follow-up appointments usually made on a quarterly basis. During each interaction interim history was obtained and physical examination was performed. A careful review of interim brain MRI studies and a comparison with the pretreatment imaging was always performed. Median follow-up was 9 months.

Treatment results

The 1- and 3-year actuarial survival was 33% and 10%, respectively. The median survival for all patients was 9.2 months. It ranged tram a law of 5.8 months for lesions, which included sarcoma and colon carcinoma, to a high of 17 months for those with breast cancer (Table VI). The median survival for patients with melanoma was 8.3 months. The best median survival obtained in patients with adenocarcinoma of the breast was likely related to more effective chemotherapy available for this disease resulting in a better control of extracranial tumor. A good palliative benefit or stable quality of life in asymptomatic patients was obtained in 80% of those treated. Patients with lower (<70) score on the Karnofsky scale bad a lower median survival when compared with those presenting with higher (>70) scores, $p=0.0001$. The status of systemic disease had an important influence on survival. Patients with inactive or controlled systemic disease had a median survival of 12 months as compared to a median survival of 7 months for those with active systemic disease, $p=0.02$. The number of metastatic lesions in the brain did not have a significant influence on survival while the total intracranial tumor volume was an important predictor for survival, $p=0.02$. Local tumor control in the treated site depended on the tumor volume being >90% for patients with smaller (<3 cm^3) lesions and <80% for those with larger (>3 cm^3) lesions. Tumor response to GK SRS was a durable event with only few patients manifesting a relapse in the treated site. About 25% of patients had a relapse elsewhere in the brain and were considered for GK if they met the criteria established for the patients treated de novo. The median time to tumor recurrence outside of the GK treated volume was 12 months. Treatment outcome in this group of patients was as good as in those treated primarily. Important details on salvage treatment outcome in the patients who relapsed bas been presented elsewhere [23].

About 70% of the study patients are known to have died. The pattern of failure in patients with melanoma metastatic to the brain was distinctly different from those with other histological diagnosis. In the 241 melanoma patients the cause of death was due to a progressive systemic disease, in 42% due to CNS causes and in 8% the cause of death was not known. In the 236 patients with the other histological diagnoses, systemic disease was a cause of death in 70% while deaths due to CNS causes was seen in 23%. The mode of death in patients dying of CNS causes was a progressive disease outside of GK treated volume including meningeal cranial or spinal carcinomatosis. Very few (5%) patients died due to cerebral hemorrhage.

Because of the well-known difficulty in accurate measurements of intracranial tumor volume, we elected to conduct a special study [27]. This study was limited to 122 consecutive patients with intracranial metastatic melanoma treated with GK SRS between 1994 and 1999. A special effort was made to measure pretreatment and post treatment tumor volume accurately. This included

patients with irregular tumor outline. Relevant MRI images were scanned with the use of color film scanner with a resolution 600 to 1200 dpi. Subsequently, tumor images were reconstructed using GammaPlan software (Electa Instruments).

Of the 122 study patients, 61 (50%) had solitary tumors, 26 (21%) had 2 lesions, 18 (15%) had 3 lesions and the remaining 17 (14%) had 4 or more lesions. A median tumor volume was 0.8 cm^3 and a mean volume was 2.62 cm^3. Median radiation dose was 20 Gy defined to a median isodose line of 60%. The overall 1-year actuarial survival was 26% with a median survival of 7 months. The median survival from the time of diagnosis of brain metastasis was 9.1 months and from the original diagnosis of cutaneous melanoma, 47 months. A good correlation was seen between survival and the total intracranial tumor volume, p=0.0007. No such correlation existed between the number of metastatic lesions and survival. In multivariate analysis, total intracranial tumor vo1ume and the status of systemic disease (active vs. inactive) were the only significant factors predicting survival with p=0.003 and 0.0065, respectively. Tumor location infratentorial vs. supratentorial had borderline significance (p=0.056) in predicting survival, and surprisingly, favored patients presenting with infratentorial tumors. Performance status, patient gender, number of intracranial lesions, patient age and WBI were not significant factors predicting survival.

Of the 122 patients, 86 (70%) are known to have died. Death due to progressive systemic disease was noted in 46%, due to CNS causes in 34% and the cause of death was unknown in 20% of patients.

GK SRS was very tolerated by the study patients. Symptomatic, focal necrosis requiring craniotomy was an uncommon event seen in < 5% of patients.

Discussion

Stereotactic radiosurgery helped to redefine the management of patients with many intracranial and in recent years also extracranial tumors (5). This treatment, which is being given on an outpatient basis, clearly demonstrated in many studies excellent results in terms of a high incidence of local tumor control, good quality of life with a law incidence of toxicity and survival comparable to that obtained with a conventional surgery [1, 6, 8, 10, 11, 13, 22, 25, 27, 28-32]. It is apparent that SRS should be offered to properly selected patients, as an indiscriminate use of this modality may compromise patient well-being or even decrease their survival. SRS has become a treatment of choice in patients with smaller acoustic neuromas, meningiomas as well as in those with residual or recurrent pituitary adenomas particularly if the tumor is invading the cavernous sinus [6-10].

Brain metastasis represents the most common CNS tumor [33, 34]. In the US, over 200,000 patients are diagnosed annually with this manifestation of metastatic disease [11, 29, 33-39]. Extrapolating from these data and assuming a similar incidence of metastasis in Poland, the number of patients presenting annually in that country should be well over 35,000. In the past, selected patients with brain metastasis were treated with surgical excision and/or WBI [34-40]. Median survival of patients treated with WBI was <4 months [25, 26, 36-38]. Patients treated with surgery had a longer median survival, but this was very likely due to patient selection process rather than a superiority of surgery over WBI [34, 35]. Patients treated with WBI and surviving > 6 months had a probability of development of late complications of radiotherapy resulting in a sharp decrease of quality of life. Additionally, WBI requires multiple visits for daily treatments. During the past decade, patients with brain metastasis became the most frequent indication for SRS. The use of radiosurgery in this patient population resulted in a substantial improvement in median survival over that obtained with the use of WBI [11-14, 22, 24-32]. Treatment toxicity has been lower than that of WBI or craniotomy. It is obvious, however, that radiosurgery is a suitable treatment only for properly selected patients.

USC experience in the treatment of brain metastasis is of interest. The unequivocal demonstration of the importance of the total intracranial tumor volume on survival and local tumor control bas major management implications. We recommend a routine MRI screening of high-risk patients for development of brain metastasis. This is in order to diagnose metastatic disease in its early stage with a law total intracranial tumor volume and prior to the patient development of frequently distressing signs and symptoms of CNS involvement. Early application of SRS is expected to result in this patient population in an improved survival and maintenance of good quality of life.

Frameless SRS is clearly going to represent the future of radiosurgery. In addition to similar indications for treatment within the cranial cavity as those for GK or linear accelerator based systems, CK will open all other extracranial sites, which till now were to a large extent unavailable for SRS. Solitary metastasis or small primary lesions of the lungs represent an obvious indication for frameless SRS. The same is true for selected patients with liver or adrenal metastasis. It is expected that some patients with residual or recurrent carcinoma of gastrointestinal and genitourinary tract following surgical resection will become a new and important indication for CK SRS. Multiple phase I-II clinical trials are currently under way in a number of medical centers. These trials will help to better define the role of CK in the management of patients with malignant and benign tumors as well as same functional disorders.

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Zbigniew Petrovich, MD, Cheng Yu, PhD
Department of Radiation Oncology
USC School of Medicine
1441 Eastlake Avenue, Room G356
Los Angeles, Califomia 90033-1086, USA

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