Gamma Knife Radiosurgery in the Management of Brain Metastases

Beyin Metastazlarının Tedavisinde Gamma Knife Işın Cerrahisi

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Abstract: To report our experience with a series of consecutive patients with brain metastases, who underwent gamma knife radiosurgery during a 3 year period and to assess the prognostic significance of primary cancer type, number of intracranial lesions, and tumor location with regard to survival. We also examined the value of adjuvant whole brain irradiation for prolonging survival in this patient group. The records of 96 patients with 233 lesions were retrospectively reviewed. Primary cancer type, number of lesions per patient, and lesion volume, location and enhancement pattern were assessed in each case. The cases were divided into various subgroups, and rates of response to radiosurgery and survival times were compared using Kaplan-Meier analysis and the log rank test. The average follow-up period after radiosurgery was 36 weeks for all patients. Local tumor control was achieved in % 88 of the cases. When stratified to subgroups, patients with breast cancer demonstrated a longer survival compared to patients with renal cell cancer. Also patients with single metastases survived significantly longer than patients with 3 or more metastases. The patients who underwent adjuvant whole brain irradiation did not survived significantly longer than other patients. Gamma knife radiosurgery is an effective modality in the treatment of metastatic disease to the brain. Survival of the patients were effected by; primary cancer type, systemic disease status, and number of intracranial lesions. Adjuvant whole brain radiotherapy provides no significant survival benefit.

Key Words: Gamma knife, Radiosurgery, Brain metastases

Özet: Üç yıllık bir dönemde, gamma knife ile tedavi edilen beyin metastazlı hastaları sunmak ve; kanser türü, intrakranial lezyon sayısı, tümörün yeri ve tüm beyin ışınlanması gibi faktörlerin, bu hastaların yaşam süresi üzerindeki etkilerini araştırmak. Toplam 233 lezyonu bulunan 96 hasta, geriye dönük olarak tarandı. Kanserin türü, lezyon sayısı, lezyon hacmi, lezyon yerleşimi ve lezyonun kontrast tutma özellikleri kaydedildi. Lezyonların ışın cerrahisine yanıtları araştırıldı ve çeşitli alt grupların yaşam süreleri Kaplan-Meier analizi ve log-rank testi kullanılarak karşılaştırıldı. Tüm hastalar için ortalama takip süresi 36 hafta idi. Lokal tümör kontrolü vakaların % 88 inde sağlandı. Alt gruplara ayrıldığında, meme kanseri tanısı olan hastaların, böbrek kanseri tanısı olan hastalara kıyasla daha uzun yaşadıkları görüldü. Ayrıca tek metastazı bulunan hastaların yaşam sürelerinin, 3 ve daha çok metastazı bulunan hastalara kıyasla daha uzun olduğu görüldü. Ek tüm beyin ışınlanmasının yaşam süresi üzerinde herhangi bir pozitif etkisi saptanmadı. Gamma knife ışın cerrahisi, beyin metastazlarının tedavisinde etkili bir yöntemdir. Kanserin türü, sistemik hastalığın durumu, ve intrakranial lezyon sayısı hastaların yaşam süresini etkilemektedir. Tüm beyin ışınlanması herhangi bir ek yarar sağlamamaktadır.

Anahtar Kelimeler: Gamma Knife, Işın cerrahisi,

INTRODUCTION

Brain metastases represents a grave sign during the course of systemic cancers and up to % 50 of the patients dying from cancer have brain metastases in autopsy series (24). Many centers have adopted gamma knife radiosurgery as the treatment of choice for brain metastases. As of 1997, 17 221 cases are treated worldwide (27). Radiosurgery provides local tumor control, improved quality of life, and prolonged survival (3, 10, 20) while providing lower morbidity and reduced cost compared to conventional surgery(21).

In this study, we report our experience in a consecutive series of patients treated during a 3 years period using gamma knife radiosurgery. The aim was to determine the effects of primary cancer type, number of intracranial lesions, tumor location, and the utility of adjuvant whole brain irradiation (WBI) on survival time.

MATERIALS AND METHODS

A consecutive series of 96 patients with brain metastases who were treated between October 1997 and September 2000, were retrospectively analyzed. All patients presented with a confirmed histological diagnosis of cancer. Diagnosis of metastatic brain tumors were based on imaging findings. All the patients chosen for radiosurgical intervention had a Karnofsky Performance Scale score of 70 or more. Patients with lesions greater than 4 cm in diameter and lesions with significant mass effect did not underwent radiosurgical intervention, but were referred for surgical intervention.

Ninety six patients with 233 lesions were treated during 109 sessions. 58 patients were male (% 60), and 38 were female (% 40). Average age of the patients was 58 years with a range of 31 to 82 years. Primary cancer type of the patients included; non-small cell lung cancer in 55 (% 57), breast cancer in 11 (% 12), renal cell cancer in 6 (% 6), colorectal cancer in 6 (% 6), melanoma in 5 (% 5), small cell lung cancer in 2 (% 2), and other cancer types in 11 (% 12).

Patients were admitted in the morning of radiosurgery. Leksell G stereotactic frame (Elekta Instruments, Inc., Atlanta, GA) was placed under local anesthesia and the patients underwent high-resolution stereotactic magnetic resonance imaging (MRI). Treatment planning was performed using GammaPlan treatment planning software (Elekta). The median radiosurgery dose delivered to the tumor margin was 16 Gy ranging between 10 to 25 Gy. This was prescribed to the %40 - %80 isodose line, which corresponded to the lesion periphery as defined by using contrast enhanced MRI. Patients were discharged on the next morning and every patient received a single dose of 16 mg methylprednisolone. All patients with supratentorial lesions were treated with a regimen of antiseizure medications.

Follow-up images were performed every 2 months following radiosurgery. Tumor volume was calculated for base-line and follow-up MRIs by measuring the the maximum diameter of the enhancing metastatic lesion in three orthogonal planes (anterior-posterior [d1], transverse [d2], and superior-inferior [d3]) and applying the findings to the formula [volume = 4/3 x P (d1/2 x d2/2 x d3/2)] for the volume of an ellipsoid (23). Also the enhancement pattern was noted for each lesion as homogenous or heterogenous (including rim-enhancing and patchy) by the same reader.

Treated lesions were grouped according to its change in volume relative to the base-line volume; *good response* indicated >% 50 volume reduction, *partial response* indicated a volume reduction of % 25 to % 50, *minimal response* indicated <% 25 volume reduction, or upto <% 25 volume increase with the radiological evidence of central necrosis, and *tumor growth* indicated >% 25 increase in tumor volume. Tumors with good, partial, or minimal responses were considered to be under local control. Patients with tumor growth and patients with new lesions underwent repeat radiosurgery if they continued to meet the initial criteria for radiosurgery, otherwise they were referred for surgical intervention or conservative therapy.

Fifty six patients have received whole-brain radiotherapy at some time during their disease course, either before or following radiosurgery. Our protocol is to initially perform radiosurgery only, and reserve whole-brain radiotherapy for polyfocal CNS disease that can not be treated with radiosurgery alone. Therefore only 4 patients out of 56 has received whole-brain radiotherapy in our clinic and rest were treated in other institutions. The median dosage for these patients was 3000 cGy with a median of 15 fractions.

Survival was measured from the time of radiosurgical treatment. Survival rates was computed by Kaplan-Meier analysis using the Statview software. Two curves were compared using the log-rank test, and $p < 0.05$ was considered to be statistically significant.

RESULTS

The average follow-up period after radiosurgery was 36 weeks for all patients, ranging from 4 to 176 weeks. Fifty-eight patients (% 60) were known to have died at the end of the recording period. Average survival of the deceased patients was 24 weeks. The cause of death was due to intracranial lesions in 8 of the patients, in which local control could not be achieved, and rest were due to the systemic disease. Overall survival is demonstrated in Figure 1.

The average baseline lesion volume was 3825 mm3, ranging from 24 to 17995 mm3. Location of the tumors was as follows; 72 (% 31) in the parietal lobe, 46 (% 20) in the frontal lobe, 42 (% 18) in the cerebellum, 29 (%12) in the temporal lobe, 19 (% 8) in the occipital lobe, and 25 (% 11) in other locations.

Local tumor control was achieved in 205 (% 88) of the 233 metastatic lesions. Of these 205 lesions; 119 (% 51) demonstrated a good response, 54 (% 23) demonstrated a partial response, and 32 (% 14) demostrated a minimal response. Tumor growth was noted in 28 (% 12) of the lesions.

The effect of the number of lesions on overall survival was assessed. Fifty patients (% 52) presented with single intracranial metastases, 15 patients (% 16) presented with two metastases, and 31 patients (% 32) presented with three or more metastases. There was a trend toward shorter survival as the number of lesions increased. When stratified to two groups with patients presenting with single metastases compared to patients presenting with 3 or more (multiple) metastases, statistical significance was demonstrated. (Fig 2)

Contrast enhancement patterns of the lesions was also noted. Seventy-four (% 32) of the lesions was enhancing homogenously, and 159 (% 68) of the lesions were enhancing heterogenously, either in a rim-enhancing pattern or a patchy pattern. Tumor response to radiosurgery seemed to be better with homogenously enhancing lesions. Forty-five (% 61) of the homogenously enhancing lesions demostrated good response compared to seventy-four (% 47) of the heterogenously enhancing lesions that have demonstrated good response. (Fig 3)

Primary cancer type was one of the factors that affecting survival. To demonstrate this relationship, patients presenting with breast cancer was compared with patients presenting with renal cell cancer. Eleven patients presented with breast cancer, 5 of them died, and the average follow-up time was 46 weeks for 11 patients. Six patients presented with renal cell cancer, 5 of them died, and the average follow-up time was 15 weeks for 6 patients. When compared statistically, patients with renal cell cancer demonstrated a significantly shorter survival. (Fig 4)

Posterior fossa tumors demonstrated a lower local control rate (% 74) when compared to the supratentorial tumors (% 91). To assess the significance of lesion localization on survival, patients with single supratentorial lesion were compared with patients with single infratentorial lesion. Thirty-seven patients presented with single supratentorial tumor, 19 of them died, and average follow-up time was 43 weeks. Fourteen patients presented with single infratentorial tumor, 8 of them died, and average follow-up time was 39 weeks. When compared statistically, no significant difference on survival was demonstrated. (Fig 5)

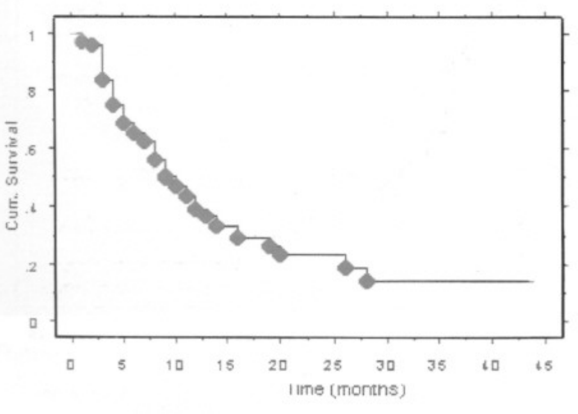


Figure 1: A Kaplan-Meier survival curve showing overall survival for all patients.

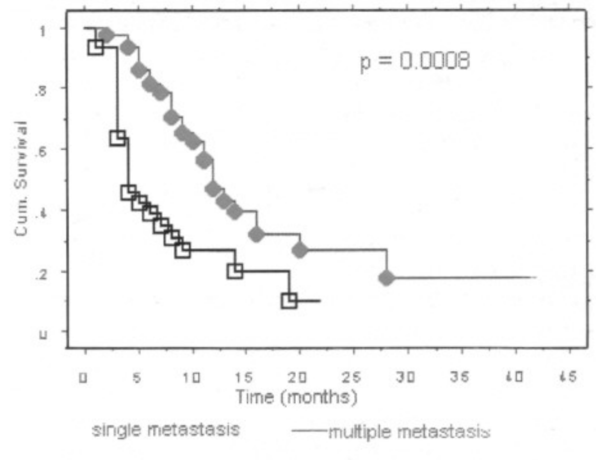


Figure 2: The effect of number of lesions on survival time.

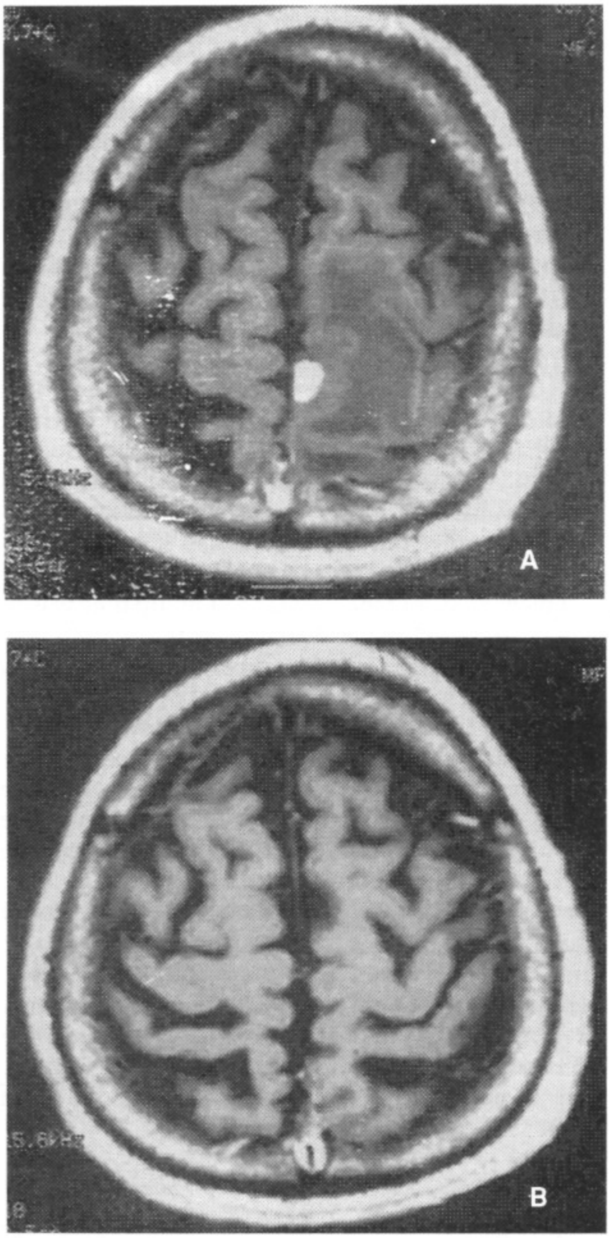


Figure 3: MRI images of a homogeneously enhancing metastatic lesion.
-**A**; 5 days prior to radiosurgery
-**B**; 16 weeks after radiosurgery

The effect of whole-brain radiotherapy on overall survival was assessed. Forty patients underwent only radiosurgery and 56 patients received whole-brain radiotherapy, in addition to radiosurgery, at some time during their disease course. When compared statistically, no significant difference on survival was noted between two groups. In fact, patients who underwent only radiosurgery demonstrated a slightly better survival but the difference was insignificant. (Fig 6)

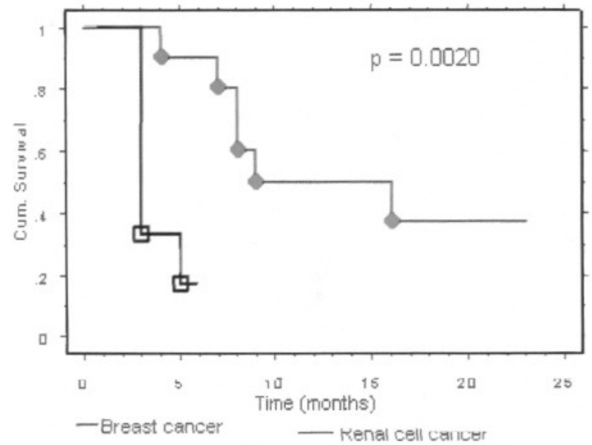


Figure 4: The effect of primary tumor type on survival time.

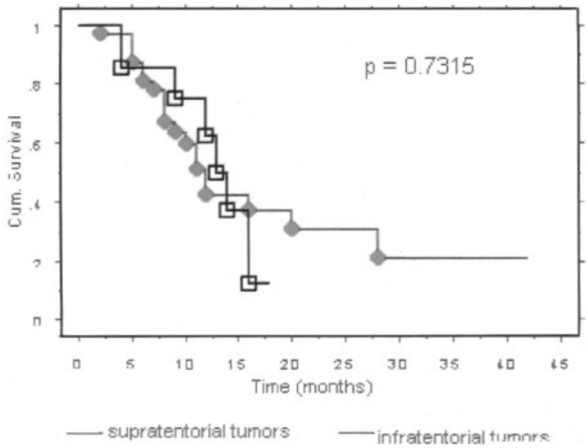


Figure 5: The effect of tumor location on survival time.

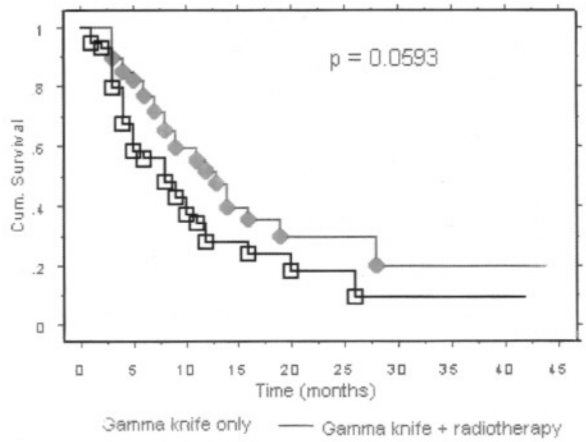
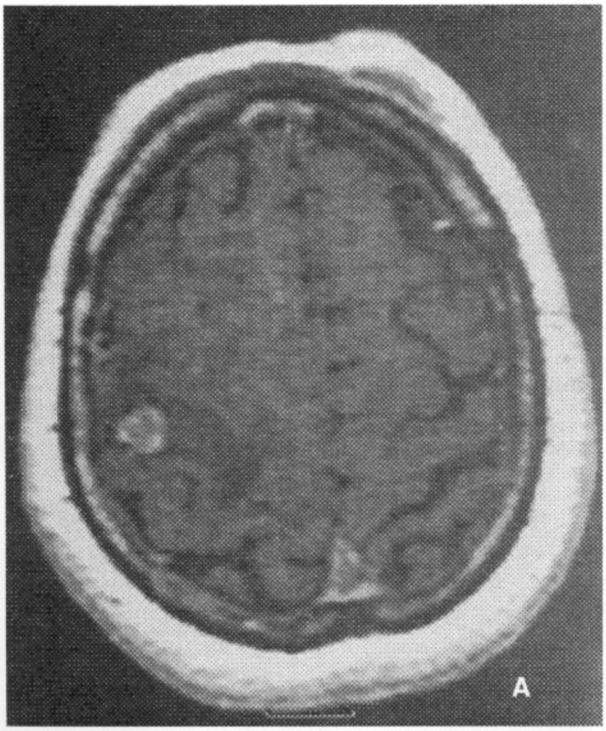


Figure 6: The effect of whole-brain radiotherapy on survival time.



Radiosurgery was well tolerated by all the patients. There were no procedure related mortalities. None of the patients demonstrated evidence of radionecrosis outside the radiosurgical treatment margin. Only one patient , who were treated with the diagnosis of melanoma, had a seizure within the first 24 hours of treatment, computerized tomography (CT) of the patient revealed intratumoral bleeding and the patient underwent emergency surgical decompression.

Local tumor control could not be achieved in % 12 of the cases. Four of the patients with tumor growth underwent repeat radiosurgery for the same lesion, because the tumor was still smaller than 4 cm and the patient was clinically stable. Local control was achieved with repeat radiosurgery in 3 patients. (Fig 7) Rest of the patients were referred for surgical intervention or conservative therapy, depending on the clinical picture.

DISCUSSION

Gamma knife is a neurosurgical tool developed in late 1960s by Lars Leksell, MD. Although it was originally created to serve for functional neurosurgery,

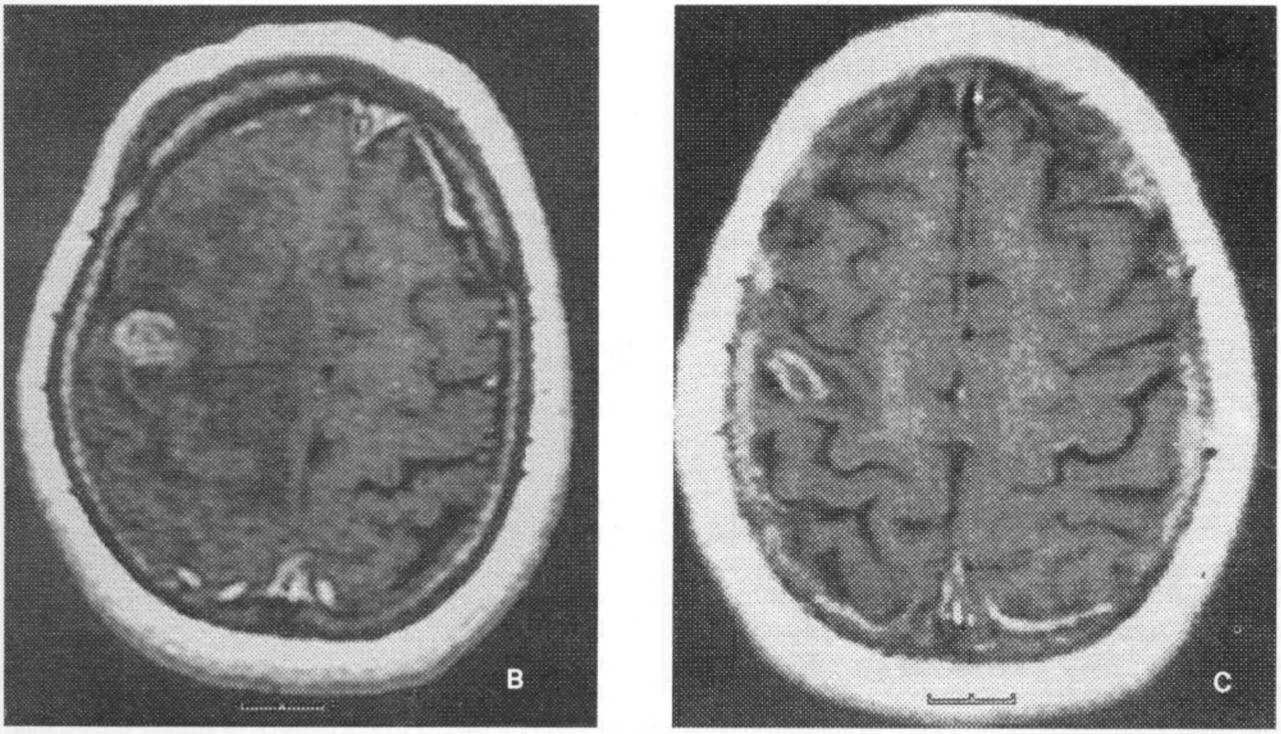


Figure 7: MRI images of a tumor for which repeat radiosurgery is performed.
-A; Peri-operative MRI image of the lesion in the initial procedure
-B; 24 weeks after radiosurgery, note the tumor growth
-C; Repeat radiosurgery is performed for the same tumor and images obtained 8 weeks after the second session demonstrates local control.

by 1970s, arteriovenous malformations (AVM) became the major indication. From 1968 to 1997, 17 442 AVM cases, which constitutes %22 of the all cases, were treated with gamma knife world-wide (27). In early 1990s, gamma-knife became an option in the treatment of metastatic disease to the brain (10). Metastatic brain tumors were particularly well suited for the treatment with gamma knife, because the lesion was usually small, well circumscribed, spherical and have radiographically distinct enhancing margins (20). Over the years, gamma knife gained a wide acceptance in the treatment of brain metastases, and although a relatively new indication, 17 221 cases have been treated upto 1997 world-wide, which constitutes %21.6 of the all cases . Today, brain metastases is the most common indication for gamma knife radiosurgery (27).

The goals of radiosurgery in the treatment of brain metastases include; local tumor control, improved quality of life, and prolonged survival (3, 10, 20). Although the exact mechanism of action of radiosurgery on brain tumors are not known, a number of theories are proposed. Hawighorst et al. stated that, radiosurgery distrupts the microvascular supply to the tumor and therefore reduces the tumor blood flow over time (15). Also Tsuzuki et al. proposed that the induction of apoptosis by gamma radiation in proliferating cells may be responsible for the effect of gamma knife on tumors (29). Additionally, on the contrary to WBI, the cellular response of gamma knife is cell cycle independent (16). Therefore the objective of gamma knife is not necessarily inducing tumor necrosis by using gamma radiation. These findings allowed neurosurgeons to use lower doses, which resulted in similar local tumor control rates but fewer complications (27). Although the mechanism is not exactly known, it is very well recognized that radiosurgery is effective in the treatment of brain metastases. Local tumor control rates ranging from % 82 to % 96 were reported in several previous studies (1, 3, 7, 8, 11, 17, 19, 22).

Although the local tumor control rates are high, survival is still unsatisfactory. Radiosurgery provides local control and only a small proportion of patients die due to intracranial disease. But the major cause of death is the systemic disease. Prognostic factors for brain metastases have been the scope of several studies and some classifications have been proposed. Gaspar et al. analyzed 1200 patients and developed a recursive partitioning analysis (RPA) classification and proposed three classes in descending prognostic expectancy, in which the parameters were; age, Karnofsky performance status (KPS), systemic disease status, and evidence of extracranial metastases (13). Weltman et al. proposed the score index for radiosurgery (SIR) in brain metastases in which the parameters were; age, KPS, sytemic disease status, largest intracranial lesion volume, and number of intracranial lesions (31).

Primary cancer type is one of the important prognostic factors in patients with metastatic brain tumors. Chen et al. stated that the survival of the melanoma patients was significantly shorter compared to the non-melanoma patients (6). In this study, the patients with breast cancer were compared with the patients with renal cell cancer. Patients presenting with renal cell cancer demonstrated a significantly shorter survival.

Another important prognostic factor in this study was the number of lesions. Patients presenting with single metastases demonstrated a significantly longer survival when compared to patients presenting with 3 or more metastases. This finding was comparable with previous reports; Breneman et al. reported that, in their series, patients with 1 or 2 metastases had significantly improved survival compared to patients with 3 or more metastases (5). Chen et al. stated that, survival was markedly shorter for patients with 4 lesions when compared to patients with single lesion, but no statistical significance was demostrated (6).

In this retrospective study, one of the outcomes was the relatively low tumor control rates of the infratentorial lesions compared to the supratentorial lesions, which was probably because of administration of lower doses due to the proximity of the brain stem. Therefore the effect of the localization of the tumor on survival was assessed. Patients presenting with single supratentorial lesion were compared with patients presenting with single infratentorial lesion. There was no significant difference on survival.

Another outcome was the relatively higher good response rates of homogenously enhancing lesions. Peterson et al. , depending on the previous studies (14, 18, 30), hypothesized that the homogenously enhancing lesions respond better to radiosurgery, because the uniform contrast enhancement reflects the uniform oxygen distribution throughout the mass, and this, in turn, promotes a uniform response to radiation treatment (23). A pitfall about this subject can be, that the smaller lesions tend to enhance homogenously, probably due to lack of intratumoral necrosis, and the lesion volume itself is an important factor of response to radiosurgery, as well as a significant prognostic factor of survival (6).

There is no debate about whether repeat radiosurgery should be done for the newly appearing lesions, as long as they are within the treatment limits of radiosurgery (6, 32). Patient in Figure 8 is a neurosurgeon who presented with the diagnosis of non-small cell lung cancer and metastatic disease to

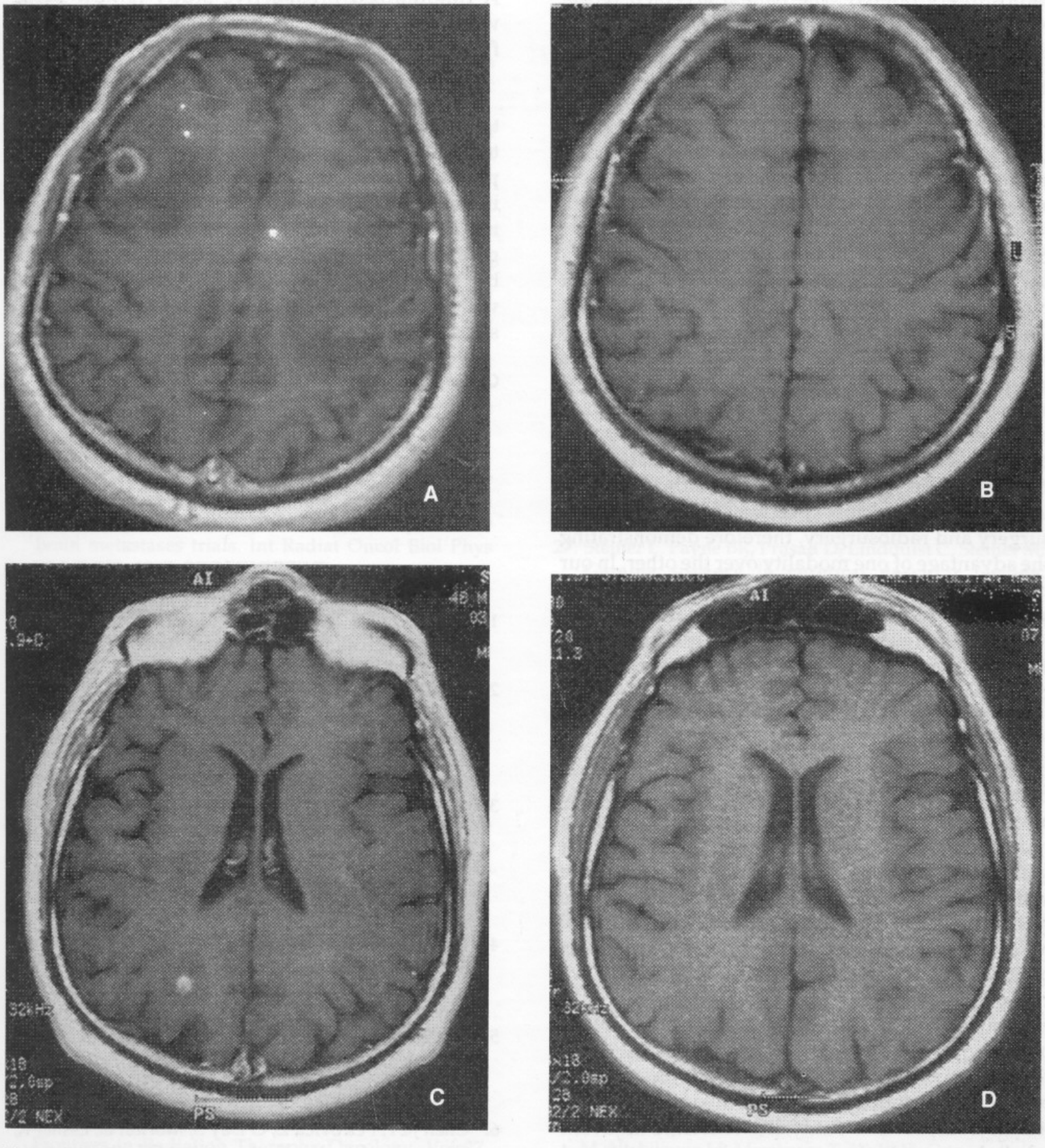


Figure 8: MRI images of a patient who presented with non-small cell lung cancer and underwent radiosurgery twice for the treatment of the metastatic disease to the brain.

-A; Peri-operative MRI image of the lesion in the initial procedure

-B; 16 weeks after radiosurgery, note that the lesion has disappeared

-C; 24 weeks after radiosurgery, a new lesion was detected and repeat radiosurgery was performed

-D; 8 weeks after the second session, local tumor control was confirmed.

the brain. After the radiosurgery, lesions demonstrated a more than % 50 decrease in volume. During his follow-up new lesions was noted, and repeat radiosurgery offered. The patient accepted repeat radiosurgery and local control has been achieved on the new lesions.

The choice between open surgery and radiosurgery is still controversial. Bindal et al. states that surgery is superior to radiosurgery and surgically treated patients survive longer and have a better local control (4). On the other hand, Alexander et al. postulates that radiosurgery provides local control rates equivalent to those of surgical series and it is also the ultimate treatment modality in multiple and surgically inaccessible leisons (2). Mehta et al. proposes that radiosurgery and surgery has similar outcomes, but surgery results in 1.8 fold increase in cost, therefore radiosurgery is a more cost-effective procedure (21). The main reason of this debate is that individual retrospective series of radiosurgery and surgery is being compared, and the survival times are found similar. However, there is no randomized, prospective study comparing surgery and radiosurgery, therefore demonstrating the advantage of one modality over the other. In our clinic, surgery is reserved for patients with single, accessible lesions, who present with signs of increased intracranial pressure (ICP), or patients with tumors larger than 4 cm in diameter presenting with peritumoral edema and mass effect.

Whole brain irradiation has occupied an important place in the primary treatment of brain metastases for many years. Several clinics prefer to administer whole brain irradiation first, an then radiosurgery as a boost therapy. Also because of the fact that, whole brain radiotherapy is a much more wide spread treatment modality, many of the patients receive whole brain irradiation before they are refferred to a radiosurgery center. To assess the effect of adjuvant whole brain therapy on survival we compared the patients who underwent only radiosurgery with patients who received both whole brain radiotherapy and radiosurgery. Statistically there was no significant difference on survival between two groups. This was comparable with the results of a previous study (6). Therefore adjuvant whole brain radiotherapy provides no additional benefit on survival. Only rationale for the use of whole brain irradiation can be the control of micrometastasis that may be present remote to the primary lesion. Upto date, several reports have postulated that adjuvant WBI improves the freedom from new metastases, but only Pirzkall et al. could demonstrated a weak significance (9, 12, 25, 26, 28). A randomized prospective study is now being witheld in our clinic to assess the effect of WBI on freedom from new metastases.

In conclusion, gamma knife is an effective treatment modality for brain metastases. Current trends in surgery emphasize less traumatic and more physiologic procedures. This can be achieved by increased skill and new technology. Although it does not provide the thrill and glamor of open surgery, gamma knife is a neurosurgical tool, and it should be the first line of treatment in patients presenting with brain metastases which is not associated with signs of increased intracranial pressure.

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