Volumetric follow up of brain metastases: a useful method to evaluate treatment outcome and predict survival after Gamma Knife surgery?

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Object. Brain metastases are diagnosed in 20 to 40% of all cancer patients and are associated with a considerable drop in life expectancy and often also in quality of life for these patients. Several treatment options are available including surgery, chemotherapy, whole-brain radiotherapy, stereotactic radiotherapy, stereotactic radiosurgery, and Gamma Knife surgery (GKS). However, management of brain metastases still presents a challenge and there is no general consensus on the best treatment strategy. The aim of the authors’ study was to further evaluate the efficacy of GKS in the treatment of brain metastases and to evaluate the predictive value of volumetric tumor follow-up measurement.

Methods. Consecutive patients with controlled systemic cancer and variable numbers of brain metastases were included in this prospective study. Patients with severe symptoms of brain compression underwent surgery before GKS. Each follow-up examination included a thorough neurological examination and a neuroradiological quantitative volumetric tumor analysis. A total of 300 consecutive patients (mean age 58 years) with 703 brain metastases were treated between December 1998 and October 2005. The mean total tumor volume (TTV) was 2.1 cm³. The overall local tumor control rate was 84.5%. In 79% of all treated metastases a mean TTV reduction of 84.7% was achieved using a mean prescription dose of 21.8 Gy. Only few, mostly mild, side effects were observed during the mean follow-up period of 12.7 months. The overall mean progression-free survival period was 9.4 months. There was a statistically significant difference in survival of patients with one compared with multiple metastases, regardless of the histological type and preceding treatment.

Conclusions. Gamma Knife surgery is a safe and effective treatment for patients with brain metastases regardless of the history of treatment and histological tumor type. It achieves excellent tumor control, significant TTV reduction without causing severe side effects, and accordingly, preserves quality of life. Volume changes after GKS did not serve as a predictor for treatment outcome and survival.

KEY WORDS • brain metastasis • volume reduction • Gamma Knife surgery

Brain metastases are diagnosed in approximately 20 to 40% of all patients with cancer and thus represent the most common intracranial tumor. The diagnosis of brain metastases is an indicator for a considerable decrease in life expectancy and QOL even for patients with controlled systemic cancer. To improve treatment strategies for these patients several studies have been performed to identify prognostic factors to assist in deciding how aggressively a patient should be treated. Optimality management of these brain lesions still represents a challenge because treatment options are limited and the appearance of brain metastases varies considerably. Different primary cancers show different patterns of intracranial metastatic spread; however, not only the locations but the number of intracerebral metastases mainly depend on the type of primary cancer. Several treatment modalities for brain metastases have been developed over the last four decades, with the goal being to improve the local control of these tumors. However, QOL in patients with a life expectancy of only a few months is equally important as achieving prolonged survival. Metastatic brain lesions may be treated using several treatment modalities including resection, chemotherapy, WBRT, stereotactic radiotherapy, stereotactic radiosurgery, and GKS. A multimodal therapy is most commonly used. Even though refinements of available treatment modalities have achieved higher locoregional control of brain metastases, the overall survival of patients with metastatic brain lesions has not changed considerably over the past three decades. Treatment of brain metastases has many facets due to the
Clinical Material and Methods

Patient Population

In a prospective study consecutive patients with brain metastases from different radioresistant primary cancers underwent treatment between December 1998 and October 2005 at the Gamma Knife Center in Krefeld, Germany. Neurological deficits present on the day of GKS were defined as presenting symptoms and neurological symptoms documented at the last follow-up examination were defined as the neurological outcome. The KPS score rather than the number of metastases was used as an inclusion criterion for treatment. Patients with a KPS score below 70 due to uncontrolled systemic disease were not entered into this study. Exceptions to this inclusion criterion, however, were patients who had a KPS below 70 due to neurological dysfunction that was caused by the brain metastases that were planned for GKS treatment and who were expected to improve after GKS of the dysfunction-provoking lesions.

Treatment and Follow-Up Protocol

All radiosurgical treatments were performed using a Leksell Gamma Knife Model C with APS. To deliver a steep dose gradient to vulnerable surrounding structures and to reach a high conformity over irregular TV shapes, a maximum number of isocenters were applied in each case. A T1-weighted 3D MP-RAGE contrast-enhanced MR imaging study was performed in all patients during each follow-up examination. Quantitative volumetric tumor analyses were conducted by two experienced neurosurgeons with either the Leksell GammaPlan V5.3 software or the CONVIS DICOM viewer–based software. For the calculation of a TV is the calculation of the pixel size from the distance of the fiducials integrated in the localizer box of the Leksell stereotactic headframe and, by that means, acquires a more accurate pixel size. To ensure that the results measured by these two programs are comparable, we scanned spheres with a volume of 1 cm³ filled with contrast medium and measured the volume using both programs. The results from serial measurements made on either system showed that the differences were less than 0.1 cm³ and therefore not significantly different.

Imaging and Tumors

Imaging before GKS included T1-weighted contrast-enhanced 3D MP-RAGE MR imaging and T2-weighted MR imaging to visualize edema surrounding a brain metastasis. A detailed quantitative volumetric tumor analysis was performed before GKS and during each follow-up examination. For the purpose of statistical analysis and grading, patients were subdivided in groups based on number of metastases (one brain metastasis, two–three brain metastases, four–six brain metastases, and > six brain metastases) TV and total treated TV (<2 cm³, 2 to <6 cm³, 6 to 10 cm³, and > 10 cm³). The minimal detectable volume was 0.1 cm³. Treatment failure was defined as an increase in TV compared with the volume before GKS. Successful treatment was defined as a lack of tumor growth or a TVR.

Quantitative Volumetric Tumor Analysis

The quantitative volumetric tumor analysis was performed using contrast-enhanced MP-RAGE MR imaging and no overlap of the slices. In patients who underwent follow-up MR imaging at our center, we used an isotropic sequence that involved a square matrix of at least 256 but usually 512 pixels. In patients who underwent follow-up MR imaging at a different center, we required MR images with a minimal matrix resolution of 256-square pixels. Using these parameters, voxels between 0.5- and 1-mm edge length are acquired with approximately 4 to 5 cubic pixels resulting in a measurable and useful volume of 10 mm³. Using the surface areas of a tumor on each individual image, which was outlined by hand and knowing the thickness of each image slice (usually 1 mm), a quantitative TV calculation was made with either the Leksell GammaPlan, version 5.3, software or the CONVIS DICOM viewer–based software.

The main difference between these programs relevant for the calculation of a TV is the calculation of the pixel size. The CONVIS DICOM viewer–based volume module uses the DICOM-header pixel information. The Leksell GammaPlan, version 5.3, software calculates the pixel size from the distance of the fiducials integrated in the localizer box of the Leksell stereotactic headframe and, by that means, acquires a more accurate pixel size. To ensure that the results measured by these two programs are comparable, we scanned spheres with a volume of 1 cm³ filled with contrast medium and measured the volume using both programs. The results from serial measurements made on either system showed that the differences were less than 0.1 cm³ and therefore not significantly different.

Volumetric Measurements

To ensure the quality of volumetric analysis in our center, we determined the error of segmentation. This was done by comparing real tumors with a volume of approximately 1 cm³. The volumes of these tumors were manually outlined by the two neurosurgeons performing all treatments and follow-up examinations in our center, and the results were analyzed. The maximum error in volumetric measurement of a 1-cm³ volume was found to be 0.95 cm³ (<10%). Because the error increases in smaller volumes, the error in a tumor with a volume of 0.1 cm³ is assumed to increase to 100% according to our findings. On the other hand, the error in volumetric measurements decreases in larger tumors, and according to our results, it would be 1% when measuring a TV of 10 cm³. Based on our findings, we set the threshold for TV changes at +/- 10%, which we consider the maximum error of manual segmentation.

Manual segmentation of a tumor is generally very time consuming because there are only simple filter algorithms available to make the process easier. These filters use a
Data Management and Statistical Analysis

The Leksell GammaPlan V5.3 was used for dose planning and TV analysis before GKS. The MeDiG3S Archive, version 1.1, was used to store and manage all clinical data and digital image data. The CONVIS DICOM viewer and GammaPlan were used during each follow-up examination for quantitative volumetric analysis. Microsoft Excel 2003 and SPSS, version 12.0, were used to perform statistical analyses and to plot graphs. Statistical tests included the Kaplan–Meier method, the log-rank statistic, the chi-square test, and the Mann–Whitney U-test.

Results

Patients, Therapies, and Side Effects

Complete data in 300 patients (131 males, 169 females) were available for analysis (Table 2); the patients’ mean age was 57.8 years (median 57.4 years, range 23.8–82.9 years). Patients were followed up during a mean period of 12.7 months (median 7.6 months, standard deviation 14.2). Brain metastases of the following cancers were treated: small cell lung cancer in 14 patients (4.7%), non–small cell lung cancer in 98 (32.7%), cancer of unknown primary in five (1.7%), uterine cancer in two (0.7%), colon cancer in 12 (4%), breast cancer in 73 (24.3%), and sarcoma in one (0.3%), and miscellaneous in 15 (5%). Before GKS microsurgical tumor resection was performed in 20 patients (6.7%), WBRT was conducted in 11 (3.7%), and chemotherapy alone was undertaken in 107 (35.7%). A total of 90 patients (30%) underwent a multimodal therapy before GKS; 13 patients (4.3%) underwent microsurgical tumor resection followed by WBRT; 22 patients (7.3%) underwent surgery followed by chemotherapy, and 24 patients (8%) underwent surgery followed by chemotherapy and WBRT before GKS. Neurological examinations showed a mean KPS score of 79 before GKS and 78 at the end of the follow-up period. Symptomatic GKS-related side effects were observed in 27 patients (9%).

Tumors and Volume Reductions

A total of 703 brain metastases from various primary cancers were treated. Precocious presentation of brain metastases occurred in 12 patients (4%), a synchronous presentation of brain metastases occurred in 67 patients (22%), and in 221 patients (74%) the presentation of brain metastases was metachronous to the diagnosis of the primary cancer. Patients presented with a mean of three metastases (range one–18) (Table 3, Fig. 1).

Analyses of TVs were performed quantitatively and according to the RRC described above. Analyzing the

### Table 1

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Volume responder with shrinkage of tumor volume (&gt;10%) after GKS</td>
</tr>
<tr>
<td>II</td>
<td>Treatment responder with unchanged tumor volume after GKS</td>
</tr>
<tr>
<td>III</td>
<td>Treatment non-responder with tumor growth (&gt;10%) after GKS</td>
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</table>

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>treated patients</td>
<td>300</td>
</tr>
<tr>
<td>sex (M/F)</td>
<td>131, 169</td>
</tr>
<tr>
<td>age (yrs)</td>
<td>58.7</td>
</tr>
<tr>
<td>mean</td>
<td>23.8–82.9</td>
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</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of BMs before GKS</td>
<td>3</td>
<td>1–18</td>
</tr>
<tr>
<td>prescription dose (Gy)</td>
<td>21.8</td>
<td>14–32.6</td>
</tr>
<tr>
<td>isodose</td>
<td>150%</td>
<td></td>
</tr>
<tr>
<td>number of isocenters</td>
<td>9</td>
<td>1–36</td>
</tr>
<tr>
<td>follow-up (months) after GKS</td>
<td>12.7</td>
<td>7.6†</td>
</tr>
</tbody>
</table>

*BM = brain metastasis; NA = not applicable.
†Median value.
Table 4: Gamma Knife surgery treatment outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean KPS score</td>
<td></td>
</tr>
<tr>
<td>before GKS</td>
<td>79</td>
</tr>
<tr>
<td>after GKS</td>
<td>78</td>
</tr>
<tr>
<td>TV (cm³)</td>
<td></td>
</tr>
<tr>
<td>before GKS</td>
<td>2.1</td>
</tr>
<tr>
<td>after GKS</td>
<td>1.1</td>
</tr>
<tr>
<td>mean TVR (%)</td>
<td>84.7</td>
</tr>
<tr>
<td>TVR achieved (%)</td>
<td>79</td>
</tr>
<tr>
<td>mean progression-free</td>
<td></td>
</tr>
<tr>
<td>survival after GKS</td>
<td>9.4 (5.3)</td>
</tr>
<tr>
<td>mean overall survival</td>
<td>13 (8.3)</td>
</tr>
</tbody>
</table>

TV of brain metastases showed a mean volume of 2.1 cm³ before and 1.1 cm³ after GKS, which represents a statistically highly significant TVR (p < 0.0001). Treatments were performed using a mean prescription dose of 21.8 Gy (range 14–32.6 Gy; standard deviation 2.3) at a mean isodose of 50% applied over a mean of nine isocenters (range one–36; standard deviation 7.2). Analysis of the total treated TV (Fig. 2) showed a mean TV of 5.5 cm³ (median 3.4 +/- 6.2 cm³). Analysis of the maximum prescription dose to the tumor peripheral dose demonstrated no statistically significant effect on TVR. The overall local tumor control rate was 84.5%. The quantitative volumetric TV analysis showed that in 79% of all treated metastases a mean TVR of 84.7% was achieved (Table 4). According to the RRC, 79% of all treated brain metastases in this study were Grade I, 5.5% were Grade II and 15.5% were Grade III. The results of TVR stratified by the RRC showed a mean TVR of 2.7 cm³ for RRC Grade II tumors and a mean TV increase of 3.4 cm³ for RRC Grade III tumors.

Survival Analysis and Prognostic Factors

Overall Survival. The mean survival after the first diagnosis of systemic cancer was 49.1 months (median 35.4 months) and after diagnosis of the first brain metastasis it was 17.1 months (median 12 months).

Survival After GKS. The achieved mean overall survival (Table 4, Fig. 3) after GKS was 13 months (median 8.3 months). The mean progression-free survival was 9.4 months (median 5.3 months). A total of 87 patients (29%) died during the follow-up period. When stratified by the RRC grade, the mean survival was length 7 months (median 2.7 months) for patients with Grade I tumors, 14.6 months (median 8.6 months) for patients with Grade II tumors, and 13.4 months (median 11 months) for patients with Grade III tumors.

Prognostic Factors. As potential predictive factors for outcome and survival, we analyzed the number of metastases at the time of GKS, total treated TV, and achieved TVR. Patients with a single brain metastasis had a statistically highly significant longer progression-free survival (p < 0.0001) and overall survival (p = 0.0005) than patients with multiple brain metastases (Figs. 4 and 5). Analysis of patients with multiple brain metastases showed a statistically significant longer progression-free survival and overall survival (p = 0.026) in those with a total TV of less than 1.5 cm³ at the time of GKS regardless of the number of brain metastases (Fig. 6).

Illustrative Case

This 41-year-old woman was diagnosed with breast cancer 3 years earlier. She underwent breast surgery and local radiotherapy. Two years later she developed lymph node metastases and underwent a second breast surgery and chemotherapy. Before diagnosis of these brain metastases in this case, the patient developed a paralysis of
Volumetric follow up of brain metastases

FIG. 3. Graph demonstrating overall survival in patients treated in this study.

FIG. 4. Graph exhibiting overall survival in patients with a single and multiple metastases.

FIG. 5. Graph showing survival in patients, according to the number of metastases.

FIG. 6. Graph revealing survival in patients, according to the total treated tumor volume.

Discussion

Prognostic Factors and Treatment Paradigms

Brain metastases represent the most common type of intracranial tumors. To determine the optimal treatment for patients and for better evaluation of treatment modalities, it is essential to have reliable prognostic factors. Numerous retrospective and prospective studies have been performed to identify pertinent prognostic factors for patients with brain metastases. Gasper, et al., performed a retrospective study and introduced the recursion partitioning analysis classification to stratify patients into three different groups based on certain clinical characteristics. Several factors have been identified and confirmed in a randomized study in which the KPS score found to be the most important prognostic factor. Undoubtedly the KPS score is a significant prognostic factor and in the
present study the majority of patients treated with GKS had a KPS score of 70 or higher. However, for patients with a KPS score below 70 a differentiation has to be made with regards to the reason why it is less than 70. We also included patients with a KPS score below 70 and found that survival of these patients was not statistically significantly different than in patients with a much higher KPS score. The reason for this is the fact that patients with a reduced KPS score were only included if the lesions planned for treatment with GKS were the only reason for a KPS below 70 rather than their systemic cancer. After successful treatment of these patients, the KPS score increased above 70 and in this way had no statistical effect on the mean survival.

Time of brain metastasis presentation has been described to be another important prognostic factor. Particularly for patients with non–small cell lung cancer, it was found that a synchronous presentation, 2 months within diagnosis of the primary tumor, is in most cases associated with poor survival. In this study 22% of patients had a synchronous presentation of brain metastases, 4% had a precocious tumor presentation, and 74% had a metachronous presentation of brain metastases. This distribution has previously been described in literature. However, the time of presentation of a brain metastasis had no prognostic value in our study and there was no statistical difference in survival between these groups.

Approximately 30 to 40% of all patients with brain metastases develop only a single lesion as is typically seen in patients with adenocarcinoma of the breast, colon carcinoma, renal cell carcinoma, and in patients with thyroid carcinoma. Multiple brain metastases, on the other hand, are usually observed in patients with malignant melanomas and in patients with lung cancer, which was found to be the leading source of brain metastases. A similar distribution of metastatic spread to the brain was found in our group of patients as well. The number of brain metastases has been described as a predictor for...
survival, with a higher number of brain metastases being generally associated with a shorter survival. For most of the recommended treatment paradigms the number of metastases is an important factor representing a junction between more aggressive and palliative treatments. Our data are concordant with current literature in the fact that patients with a single brain metastasis had a statistically significant longer mean survival (p = 0.0005) than patients with multiple brain metastases. However, our results show that in patients with multiple brain metastases the total TV treated with GKS rather than the number of brain metastases had an influence on survival (p = 0.026) and could therefore serve as a prognostic factor. Patients with a TV of more than 1.5 cm³ had a statistically significant shorter survival. Similar findings have been published by Metha, et al., who showed that as tumor size increased control decreased. Based on our results, the TV before GKS could serve as a prognostic factor; however, further studies will be necessary to confirm this finding.

Even with all available prognostic factors it is still difficult to predict the course of disease for patients with brain metastases. Nevertheless, predictive factors are central because they present a guide in the decision-making process on how aggressively to treat patients, especially those with decreased QOL and considerably reduced life expectancy.

Tumor Volume Reduction After GKS

A review of literature by Prasad showed that the median survival of patients with brain metastases varied greatly in different series depending on the different tumor types but rarely exceeded 12 months regardless of the treatment modality used. The overall median survival of patients in this study was at 8.3 months and is concordant with literature. The high efficacy of GKS in the treatment of brain metastases especially compared with WBRT has previously been described. Reported local tumor control rates range from 82 to 100%, and also TVRs of brain metastases have previously been shown. Even patients with multiple brain metastases were treated successfully with GKS. Local tumor control rates after GKS were comparable to results of surgical treatment, however, with a much lower morbidity and no mortalities. Undoubtedly microsurgical treatment is essential in cases in which it is necessary to achieve an immediate decompression of neurovascular structures. Results of this study are in accordance with literature, with a local tumor control rate of 84.5% and a morbidity of only 7.3%.

Even though TVRs after GKS have been reported, quantitative volumetric analyses are rarely performed because they are time consuming. It has previously been reported that tumor size has an influence on the therapeutic ratio and it was also shown that the maximum tolerated radiosurgery dose is directly related to tumor size. However, there are few reports on the impact of reduced TV on survival after GKS. With the purpose of analyzing the predictive value of TVR on survival, a quantitative volumetric tumor analysis was performed. To define volume changes more precisely and to make results more comparable in the future, we used the RRC (Table 1) to describe TV changes. This classification is currently used as a descriptive classification, but further studies and genetic tumor analysis might change the RRC to a predictive classification in the future. According to the RRC, a mean TVR of 84.7% was achieved in 79% of all treated metastases in this study. These results are very encouraging in terms of local tumor control. However, statistical analysis showed that there was no correlation between the achieved TVR and survival of a patient after GKS, and stratification of results by the RRC showed that patients with RRC Grade I tumors had a shorter survival than those with RRC Grade III tumors.

Even though our results were encouraging, we found that the time-consuming process of quantitative volumetric tumor analysis did not prove to be as valuable for patients with brain metastases as it has previously been shown for patients with benign tumors. These results show once more that good local tumor control and even TVR do not automatically translate to better survival. If good local tumor control does not have an effect on survival, what will? In our view, more studies should be performed with the focus on one type of systemic cancer and its metastatic behavior rather than evaluating several different types of brain metastases from various primary cancers simultaneously. It seems that with the currently available treatment modalities the maximum possible survival rates have been reached and that only after improvement of systemic treatment will further progress in survival and QOL for patients with brain metastases be possible. The combination of early radiosurgery treatment and aggressive treatment of the systemic cancer can potentially improve not only QOL but possibly even improve survival rates. Nonetheless, of all the available treatment modalities, GKS remains an efficient treatment option with a low associated morbidity rate and essentially no death, and furthermore it has even been shown to be effective for tumors unresponsive to WBRT.

Conclusions

Gamma Knife surgery is a safe and effective treatment for patients with brain metastases regardless of the previous treatment and histological tumor type. The results in literature and in the present study show that local tumor control and TVRs are comparable to microsurgical tumor resection but with a much lower morbidity rate and essentially no mortality. An RRC was used to set a standard for quantitative volumetric tumor analysis and to make TVR results of studies using GKS better comparable in the future. The extent of achieved TVR was not an indicator of survival and can therefore not be used as a prognostic factor. The time-consuming process of quantitative volumetric follow up has therefore proven to be of less value for brain metastases as it is for benign tumors; however, results of this study show that it is not the number of brain metastases but rather the total TV treated with GKS that may have a prognostic value for survival of patients with brain metastases. Further studies will be necessary to confirm this finding. Based on findings in literature and this study, GKS should also be considered as a primary treatment option for patients with brain metastases even in cases of multiple metastases.

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