Analysis of long-term outcomes and prognostic factors in patients with non–small cell lung cancer brain metastases treated by gamma knife radiosurgery

MASSIMO GEROSA, M.D., ANTONIO NICOLATO, M.D., ROBERTO FORONI, PH.D., LAURA TOMAZZOLI, M.D., AND ALBINO BRICOLO, M.D.

Department of Neurological and Vision Sciences, University Hospital, Verona, Italy

OBJECT. The authors conducted a study to evaluate the long-term outcomes and prognostic factors for survival in a large series of patients treated by gamma knife surgery (GKS) for non–small cell lung cancer (NSCLC) brain metastases.

METHODS. The study is based on the retrospective analysis of clinical and radiological records obtained during a 10-year period (1993–2003), concerning 836 lesions in 504 patients. The lesions were primary in 86% and recurrent 14% of the cases; they were solitary in 31%, single in 29%, and multiple in 40%. The mean follow-up period was 16 months (range 4–113 months). The most common histological types were adenocarcinoma (51%) and squamous cell carcinoma (27%). Dose planning parameters were as follows: mean target volume 6.2 cm³ (range 0.06–22.5 cm³); mean prescription dose 21.4 Gy (range 15.5–28 Gy); and mean number of isocenters 6.7 (range one–18). Progression-free and actuarial survival curves were calculated using the Kaplan–Meier method. The main factors affecting survival were determined by unimultivariate analysis (log-rank test and Cox proportional hazard models).

Analysis of long-term outcomes seemed to confirm that GKS is a primary therapeutic option in these patients. The 1-year local tumor control rate was 94%. The overall median survival was 14.5 months, with extremely rewarding quality of life indices. The recursive partitioning analysis classification was the dominant prognostic factor.

CONCLUSIONS. Gamma knife surgery is a useful treatment for brain metastases from NSCLC.

KEY WORDS • gamma knife surgery • brain metastasis • non–small cell lung cancer

M etastatic lung carcinoma is reported to be the leading cause of death from cancer, with median survivals of 3 to 6 months.1,2,21,29,31,38,42 Regarding intracranial metastatic lesions, in most published series, brain metastases from NSCLC are undoubtedly the most frequently represented1,2,16,17,21,31,35,39,41 with few exceptions.28 In the past, treatment options in these patients have been focused essentially on symptom palliation involving WBRT and steroid therapy, because of their unavoidably grim prognosis.1,2,5,29,41,42 Today such palliative regimens are only used in cases of multifocal metastatic progression in patients with severe clinical status and short life expectancy.1,2,10,11,13,14,19,21,24,28,30,32,35,41 For solitary brain metastases or so-called oligometastatic (≤ three lesions) a more aggressive multimodality approach to the intracranial disease in patients with an adequate KPS should include surgery, stereotactic radiosurgery, WBRT, and chemotherapy. Indeed, during the last decade, stereotactic radiosurgical procedures, particularly GKS, have had considerable impact as one of the most relevant treatment alternatives for NSCLC brain metastases, essentially because of the minimal invasiveness, excellent clinical results, and limited morbidity.2,10,11,13,14,19,21,24,28,30,32,35,41

Although the effects of surgery and GKS have not yet been compared in randomized controlled trials, increasing evidence suggests that results are similar, at least as regards LTC, PFS, overall survival, and reduced incidence of neurological deaths.6,10,11,13,14,19,21,24,28,30,32,35,41

Furthermore, GKS has been shown to be as effective for NSCLC brain metastases as for metastases from small cell lung cancer;28 however, both prospective randomized trials and large-scale retrospective studies with adequate follow up are sparse.10,19,20,27 Appropriate analyses of long-term outcomes (radiological and clinical result, QOL and sequelae) as well as of the main prognostic factors (including specifically the role of RPA) are much needed.

In the current retrospective study the authors describe their 10-year experience (1999–2003) with 504 NSCLC patients harboring 836 brain metastases who underwent GKS as a primary therapeutic option. Particular emphasis is devoted to examining survival rates and QOL indexes and potentially predictive parameters.

Clinical Material and Methods

Patient Population

Between February 1993 and September 2003 816 con-
secutive patients with lung cancer (56% of all metastatic cases) were treated with GKS. Tumor histological types are listed in Table 1. The vast majority of patients with NSCLC fulfilled the eligibility criteria of our previously published modified Pittsburgh protocol.

**Study Criteria**

Study criteria were the following: 1) KPS score greater than or equal to 60; 2) estimated life expectancy of greater than or equal to 4 months; 3) no rapidly evolving intracranial mass effect; 4) three or fewer lesions with an overall volume not exceeding 20 ml; and 5) target(s) well defined on the neuroimages.

Patients meeting these criteria and attending follow-up examinations for a minimum of 4 months are the subject of this study. They were evaluated separately from patients treated palliatively and who did not satisfy these requirements. The clinical case material is summarized in Table 2.

Five hundred four patients harboring 836 brain metastases (86% primary 14% recurrent) were enrolled. The mean follow-up period was 16 months (range 4–113 months).

Stereotactic brain biopsy sampling was performed if the primary tumor was unknown or had never been histologically verified, or in presence of clinicoradiological discrepancies (7%). The endpoints of the study were stated as follows: 1) the real effectiveness of GKS in terms of LTC rate compared with incidence of local recurrences; 2) the clinical impact evaluated on the basis of the median survival and actuarial PFS; 3) the QOL as analyzed using internationally acknowledged performance scores such as the palliative index and the functional independence index; 4) the clinical and radiological impact of treatment-related sequelae according to the RTOG criteria as well as Shaw neurotoxicity classification; and 5) the causes of death, itemized as suggested by Patchell, et al. — in particular, all deaths following intercurrent illnesses, even though patients were neurologically disabled, were categorized separately from neurological deaths.

**Tumor Treatments**

Tumor treatments pre- or postoperative GKS primary are summarized in Table 3. Additional treatment options for the intracranial disease in these patients are shown in Table 4.

Neuroradiological localization of the target was performed using stereotactic computerized tomography at the beginning of the study and, later, almost invariably with contrast-enhanced thin-slice MR imaging with volume acquisition.

The dose planning parameters were as follows: mean tumor volume 6.2 cm$^3$ (range 0.06–22.5 cm$^3$), and mean margin dose 21.4 Gy (range 15.5–28 Gy), mean number of isocenters 6.7 (range one–18). In a small minority of critically located lesions, staged GKS protocols or combined strategies (GKS–WBRT) were performed.

In some cases post–GKS panencephalic radiotherapy was administered only according to specific indications. This applied to 36.1% of the cases and the indications for its use included progressive multifocal tumors and salvage treatment.

The follow-up schedule included periodic clinical examinations (every 3–4 months) with assessment of the appropriate scores, and MR image evaluation of tumor volume (computerized models). The radiological response to GKS was defined as the disappearance of the enhanced lesion, tumor shrinkage (volume reduction $\pm$ 20%), and stable disease (initial volume $\pm$ 20%). An increase in tumor size of more than 20% at the site of the radiosurgical target was classified as tumor progression if there had been no regression interval and as recurrence if there had been a regression interval.

**Statistical Analysis**

Univariate analysis (log-rank test and Cox proportional hazard models) of 11 variables was performed, considering patient (age, sex, KPS), primary tumor (oncotype, staging), brain metastasis (number, recurrence, WBRT),

### Table 1

**Summary of lung cancer histological types in 816 patients**

<table>
<thead>
<tr>
<th>Type</th>
<th>No. of Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>adenocarcinoma</td>
<td>417 (51.1)</td>
</tr>
<tr>
<td>squamous cell carcinoma</td>
<td>210 (25.7)</td>
</tr>
<tr>
<td>large cells</td>
<td>55 (6.8)</td>
</tr>
<tr>
<td>other (undefined)</td>
<td>101 (12.4)</td>
</tr>
<tr>
<td>SCLC</td>
<td>33 (4.0)</td>
</tr>
</tbody>
</table>

### Table 2

**Summary of NSCLC brain metastases in 504 patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>504</td>
</tr>
<tr>
<td>M/F ratio</td>
<td>321:183</td>
</tr>
<tr>
<td>age (yrs)</td>
<td>61.5</td>
</tr>
<tr>
<td>range</td>
<td>25–84</td>
</tr>
<tr>
<td>FU (mos)</td>
<td>16</td>
</tr>
<tr>
<td>range</td>
<td>4–13</td>
</tr>
<tr>
<td>no. of lesions (%)</td>
<td></td>
</tr>
<tr>
<td>solitary</td>
<td>31</td>
</tr>
<tr>
<td>single</td>
<td>29</td>
</tr>
<tr>
<td>multiple</td>
<td>40</td>
</tr>
</tbody>
</table>

* FU = follow up.

### Table 3

**Primary tumor treatment before and after GKS**

<table>
<thead>
<tr>
<th>Treatment (alone/combined)</th>
<th>Pre-GKS (%)</th>
<th>Post-GKS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>op</td>
<td>40.5</td>
<td>32.2</td>
</tr>
<tr>
<td>radiation</td>
<td>21</td>
<td>27.3</td>
</tr>
<tr>
<td>chemotherapy</td>
<td>36</td>
<td>53.5</td>
</tr>
<tr>
<td>no treatment</td>
<td>15.8</td>
<td>14</td>
</tr>
</tbody>
</table>

### Table 4

**Additional treatments of NSCLC brain metastases**

<table>
<thead>
<tr>
<th>Treatment (alone/combined)</th>
<th>Pre-GKS (%)</th>
<th>Post-GKS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>op</td>
<td>14.6</td>
<td>6.7</td>
</tr>
<tr>
<td>same target</td>
<td></td>
<td></td>
</tr>
<tr>
<td>different target</td>
<td>9.5</td>
<td>4.3</td>
</tr>
<tr>
<td>WBRT</td>
<td>32.6</td>
<td>36.1</td>
</tr>
</tbody>
</table>

J. Neurosurg. / Volume 102 / January, 2005
and treatment parameters (mean tumor volume, edge dose, and maximum dose). These variables were subsequently used to form the corresponding RPA classes and further analyzed.

The reference point for all statistical analysis was the date of GKS. Freedom from local progression was calculated to the date of MR image–detected local recurrences. The survival analysis was performed for both the PFS and censored data by adopting the Kaplan–Meier continuous nonparametric survival model. A stratified model with separate baseline hazards for the different metastasis types (solitary, single, or multiple), for sex, age, and the censored data over weeks constituted the initial primary input dataset. The missing data, consisting of information from a mere 5% of the total population, were previously deleted from the fitting model. Estimates of the cumulative variance and confidence limits, as well as the mean and the median survival times, were calculated. Analysis of survival differences between the groups was performed using the Wilcoxon test, which is more sensitive to early differences in the survivor

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**Fig. 1.** Graph showing local PFS in the 504 patients (836 lesions). The thicker line is the calculated probability estimate, and the dotted lines represent the 95% confidence interval. 1-year PFS was 95%.

**Fig. 2.** Graph illustrating actuarial survival curves for the three groups of brain metastases: solitary (31%), single (29%), and multiple (40%). The crosses indicate censored event times. Differences among the group with solitary lesion and the other two groups (Wilcoxon test) were statistically significant (p < 0.01). Results of single metastatic lesions were worse than those of multifocalitys.

*J. Neurosurg. / Volume 102 / January, 2005*
dataset. The statistical packages used were S-Plus and Systat.

Results

The 1-year LTC was 94% with three subsets: substantial tumor disappearance (16%), shrinkage (60%), and stable imaging (18%). The recurrence rate was 9% with a mean time to recurrence of 45 weeks. This excellent tumor control rate was invariably achieved also in specific subgroups of crucially located lesions. The 1-year actuarial PFS was 95% (see Fig. 1). The overall median survival was 14.5 months, with statistically significant differences between the group of patients with solitary metastatic lesions and those with single-multiple lesions (Fig. 2). One hundred seventy-six patients are still alive (median survival 16.8 months) and 328 patients have died (median survival of 13.1 months). It is worth stressing that actuarial survival analysis confirmed in these cases a rather unusual finding. In patients with single metastatic brain lesions the survival

Fig. 3. Graph showing actuarial survival curves for RPA Classes 1, 2, and 3 patients. The crosses indicate censored event times. The difference between RPA Class 1 group, and Classes 2 and 3 was highly significant (p < 0.0001).

Fig. 4. Graph demonstrating actuarial survival curves of NSCLC, grouped according to the primary oncotype. There was a statistically significant difference (p < 0.001) when adenocarcinoma was compared with all the other histological types.
Gamma knife surgery of NSCLC brain metastases

curve was worse than those with multiple metastases (Fig. 2). Although the difference was not statistically significant, this might indicate a possible selection bias.

The mean palliation index and functional independence index were of 53 and 50 weeks, respectively. Clinical sequelae according to the Shaw classification were 5.6%, and they never exceeded RTOG Grade 3.

The causes of death were ascertained in 253 of 328 cases and classified according to criteria described by Patchell and associates. Neurological progression accounted for 17.7% of cases (6.3% local, 11.4% distal progression), whereas systemic progression accounted for 61.8%.

The major prognostic factors were represented by: 1) RPA Class 1 compared with Classes 2 and 3 (p < 0.0001) (Fig. 3); 2) adenocarcinoma oncotype (p < 0.001) (Fig. 4); and 3) solitary lesion (p < 0.01) (Fig. 2).

Other variables, particularly the total targeted tumor volume and the edge dose, were shown to bear some predictive value but never at a statistically significant level, probably because of the eligibility constraints of the protocol.

Discussion

Brain metastases from NSCLC are unanimously considered as the most frequent intracranial metastatic disease. Their grim outlook is substantially related to the rapidly disabling course and to the significant risk of neurological death.

Historically, results with conventional multidisciplinary treatments have usually been disappointing: with mean survival times of 5 to 8 weeks when applying medical palliation regimens, 3 to 7 months after whole-brain radiotherapy, and 9 to 19 months only in selected groups of patients with favorable prognostic factors, treated with combined surgery and radiotherapy.

Stereotactic radiosurgical procedures, particularly GKS, have recently gained increasing relevance within the therapeutic armamentarium for these patients. Gamma knife surgery has been used at clinical onset of disease, at recurrence, or in adjuvant schedules after prior surgery and radiotherapy. Today, accepted indications for GKS may include a variety of conditions: 1) small to medium lesion size, surgically inaccessible solitary or single lesions, with controlled neurological evolution; 2) multifocal lesions, although the maximum number of treatable lesions is debated; and 3) salvage, palliation treatment on the basis of a reasonable (> 3 months) life expectancy.

Our experience with this large series of consecutively treated patients seems to confirm the excellent clinical results of GKS as a pivotal treatment for NSCLC brain metastases. The overall mean survival of 14.5 months and the 1-year actuarial PFS of 95% are considerably higher than most of their remaining life in an improved or stable performance status. The QOL indexes were quite rewarding, with the palliation and functional independence scores approximating the values for the median survival; in other words, the majority of patients spent most of their remaining life in an improved or stable performance status. This point has previously been raised using different QOL tests such as the Spitzer analysis.

The high LTC rate (94%) seems particularly interesting considering the reasonably long median follow-up period (16 months). A more aggressive approach to the primary tumor and to the systemic disease should probably be advocated in these patients. The overall permanent morbidity rate was low (5.6%) and never life-threatening. It was always between RTOG Grades 1 and 3.

In a retrospective study, an appropriate interpretation of these results should take into account several putative conditioning biases.

Factors affecting the rates of survival and LTC after conventional radiotherapy, stereotactic radiotherapy, and radiosurgery have been extensively investigated in the past. The paramount predictive parameters have mostly been age, stage III-A NSCLC, performance status, controlled primary disease, and no extracranial metastases. On the other hand, the size and site of the lesions and the therapeutic interval from diagnosis has seemed to be of lesser importance. The debate, however, is still open. It is shown by frequently reported uni/multivariate analyses that the list of putatively conditioning factors should include: 1) number of brain metastases; 2) timing of the spread of intracranial metastases because metachronous lesions bear a more favorable prognosis than the synchronous ones; 3) increased treatment doses; 4) limited target volumes (smaller volumes usually correlate with higher and more consistent LTC); and 5) oncotype (as confirmed in our experience, results with the adenocarcinoma oncotype are more gratifying).

The importance of these particular analyses has been emphasized by the relevant prognostic impact of RPA classification, as also stressed in these series. Indeed, RPA Class 1 patients (< 65 years of age, KPS score greater than 70, primary controlled tumor, and no extracranial metastases) have a significantly (p < 0.0001) better prognosis than those in Classes 2 and 3. The relative incidence of Class 3 patients—a small minority in our study—may deeply influence the overall profile of clinical results in terms of survival. Furthermore, criteria of radiosurgically and surgically treatable NSCLC brain metastases may be substantially different with easily understandable consequences.

We conclude, however, that the huge number of consecutively treated cases and the consistency of results over time may reliably balance such constraints.

Conclusions

Analysis of long-term outcomes seems to confirm that GKS is a primary therapeutic option in NSCLC brain metastases. The RPA classification is the dominant prognostic factor concerning the outcome of treatment.

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J. Neurosurg. / Volume 102 / January, 2005

79
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