Surgical resection and radiation therapy versus biopsy and radiation therapy in the treatment of glioblastoma multiforme

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There has been considerable controversy over the concept of treating glioblastoma multiforme with cytoreductive surgery. Therefore, a retrospective study of cases treated between 1986 and 1991 was conducted to analyze and compare the results of stereotactic biopsy followed by radiation therapy performed in 58 patients with those of surgical resection plus radiation therapy in 57 patients. In both groups, conventionally fractionated radiation (1.7 to 2.0 Gy/day) was delivered, with a total dose of 50 to 60 Gy. Biopsy was performed only in patients with tumors judged to be inoperable. These patients carried a higher surgical risk and were in worse neurological condition than the patients in the resection group.

The median survival time for the resection group was 39.5 weeks, as compared with 32 weeks for the biopsy group. This difference was not significant. The most important prognostic factor was the patient's age. The treatment variable biopsy versus resection did not reach prognostic relevance. In patients with midline shift who underwent biopsy, the Karnofsky Performance Scale score decreased in more patients during radiation therapy. The clinical status 6 weeks after surgery, however, showed no significant differences between the two groups. The comparable survival times for the two groups place doubt on the concept of treating glioblastoma multiforme with cytoreductive surgery. Presently, radiation therapy is the most effective treatment for patients with glioblastoma. There is no question that decompressive surgery followed by radiation therapy should be performed whenever necessary for severe space-occupying lesions and when it will not cause new neurological deficits.

Key Words • glioblastoma multiforme • brain biopsy • radiation therapy • cytoreductive surgery

Cytoreductive surgery to treat patients with glioblastoma multiforme has met with considerable controversy. Studies on the effectiveness of "radical" tumor resection have produced divergent results.1,10-12,14,15,21,22,30-32,38 The retrospective studies carried out to date are limited by the absence of a control group. No prospective study has been published. Therefore, the present retrospective study was conducted to analyze and compare the results of stereotactic biopsy followed by percutaneous irradiation performed from 1986 to 1991 (biopsy group) with those of surgical resection plus irradiation performed between 1986 and 1988 (resection group).

Clinical Material and Methods

The pathohistological diagnosis of glioblastoma was established using the criteria defined by Burger and colleagues.4-7 The criteria for complete irradiation were: 1) beginning radiation therapy within 3 weeks after surgery; and 2) application of a conventionally fractionated radiation dose (1.7 to 2.0 Gy/day) to a total dose of 50 to 60 Gy. Therefore, in most cases whole-brain irradiation was combined with a tumor "boost." There was no case of reoperation in the surgical group, and no patient in this study received additional chemotherapy.

All of the tumors were defined as either lobar or midline glioblastomas. Tumors of the basal ganglia and the corpus callosum were classified as midline tumors. The tumor location and clinical symptoms of both treatment groups are shown in Table 1.

Biopsy Group

Between January, 1986, and March, 1991, the diag-
agnosis of glioblastoma was confirmed by stereotactic biopsy in 133 patients. Fifty-eight patients in this group received a complete course of postoperative radiation therapy, which was carried out at various centers. The indication for stereotactic biopsy was made when the tumor was deemed inoperable due to location and/or size or when surgery was expected to pose high risks with severe neurological deficits. Forty-nine patients who received only supportive therapy and 26 patients who underwent an incomplete course of radiation therapy were excluded from this study.

Resection Group
Between 1986 and 1988, 93 patients with glioblastomas were operated on by the Abteilung für Allgemeine Neurochirurgie at the Universitätsklinik Freiburg. In 66 patients, retrospective data were obtained with respect to treatment regimen, course of the disease, and survival.

Six patients who received no or incomplete radiation therapy were excluded from the analysis. In one patient the diagnosis of glioblastoma had to be revised after a repeat histological evaluation of the biopsy specimen. Two patients died as a result of postoperative complications (pulmonary embolism and pneumonia). Thus, a total of 57 patients were included in the analysis. The period between 1986 and 1988 was selected because access to the patient data via a database was possible for this time period. The diagnostic and therapeutic procedures used complied with today's generally accepted standards.

Stereotactic biopsy technique and morphological diagnosis
After the stereotactic head ring was fixed to the patient's skull, a computerized tomography (CT) scan was obtained. The stereotactic coordinates for the target point were derived directly from the CT scan under the presupposition that the three spatial axes of the stereotactic and CT units coincide. Biopsy specimens were taken from the hyperdense and hypodense areas of the tumor along a predetermined trajectory with an average of 10 specimens per biopsy procedure.

The morphological diagnosis was made by the attending neuropathologist based on the intraoperative analysis of smear preparations and postoperative examination of the paraffin-embedded material. The subsequent pathomorphological report was the result of both procedures in all cases. Areas of necrosis demonstrated in the biopsy specimen and review of the CT findings at the biopsy site were used to distinguish between anaplastic gliomas and glioblastomas.

Technique and Extent of Microsurgery
Under the operating microscope, using either a transgyral or transtentorial approach, the tumor was first debulked from within and then removed as completely as possible. Lobar resection was not performed. Postoperative follow-up CT scans were obtained on the day of surgery to rule out space-occupying bleeding into the tumor site.

Statistical Analysis
The following covariates were entered in the analysis: prescribed treatment (resection, biopsy); age at resection or biopsy (> 60 years, ≤ 60 years); major preoperative clinical symptom (presence of seizures); duration of disease before resection or biopsy (< 3 months, ≥ 5 months); preoperative Karnofsky Performance Scale (KPS) score (≥ 70, < 70); KPS score at 1 week postoperatively; KPS score at 6 weeks postoperatively; size of tumor (largest measurable diameter on contrast-enhanced CT ≤ 5 cm, > 5 cm); presence of midline shift and tumor location (lobar, midline). Comparison of the preoperative KPS scores at 1 week and 6 weeks with the preoperative performance status indicates improvement, stability, or impairment of the clinical course under treatment.

The survival time, measured from the time of biopsy or resection, was analyzed based on the Kaplan-Meier product-limit method and the Lee-Desu statistic. The chi-squared test was used to compare the distribution of the important variables between the two patient groups with dichotomous coding. The prognostic value of the individual variables was obtained from the Cox multivariate regression analysis (stepwise inclusion of variables in the equation at p = 0.05, stepwise exclusion at p = 0.1).

Results
A total of 115 patients were included in the analysis. The biopsy and resection groups did not differ significantly in terms of patient age, major clinical symptom, duration of symptoms, or tumor size.

The mean preoperative KPS score was higher (chi-squared test = 5.527, p = 0.02), the midline was shifted in more cases (chi-squared test = 10.31, p < 0.01), and the tumors were located more often in the right hemisphere (chi-squared test = 10.3, p < 0.01) in the resec-
tion group. Midline tumors were found only in the biopsy group (14 patients) (Table 2).

According to the surgeon's impression, partial resection was accomplished in two patients, subtotal tumor removal in six patients, and complete tumor removal in 49 patients. The postoperative complications that occurred in the resection group included nonspacereoccupying bleeding into the surgical site (three patients), partial infarct of the middle cerebral artery (one patient), pneumonia (one patient), and wound infections (three patients). There was complete recovery in every case with regard to the specific complication. No patient in the biopsy group suffered postoperative impairment.

**Survival Analysis**

The median survival time for the biopsy and irradiation group (four censored events) was 32 weeks versus 39.5 weeks for the resection and irradiation group (mean follow-up period 35.6 weeks). This difference was not significant (p > 0.05, Lee-Desu statistic) (Fig. 1).

In the multivariate regression analysis, the patient's age was a statistically significant variable in predicting length of survival (p < 0.01). The treatment variable (biopsy or resection) did not reach prognostic relevance (p > 0.05). When considered as a single variable in the analysis, the preoperative KPS score appeared to have a significant effect on length of survival. However, when entered as a covariate, this factor did not attain statistical significance. Other nonsignificant variables were tumor location (lobe vs. midline and left vs. right hemisphere), tumor size, and midline shift.

In an isolated analysis of the resection group, tumor location and the left-right variable had no influence on survival time. In the biopsy group, patients with midline tumors had a shorter median survival time than patients with lobar glioblastomas; however, the difference was not significant.

**Analysis of Postoperative Clinical Course**

In the resection group, the KPS score at 1 week after surgery was improved or stable in 48 patients; nine patients showed impairment postoperatively. In the biopsy group, no patient suffered new neurological deficits after the procedure and no improvement in the KPS score was observed. Upon completion of radiation therapy 6 weeks after surgery, an improvement or stability in the performance status was determined in 42 patients receiving biopsy plus irradiation and in 34 patients who underwent resection plus irradiation (chi-squared test = 1.559, p > 0.05).

In the patients undergoing biopsy plus irradiation, the midline shift factor was an important variable, since the patients with midline shift were more likely to rate worse on the KPS during the course of radiation therapy (p < 0.05). In contrast, midline shift had no influence on the course of radiation therapy in the resection group patients. There was no relationship between tumor size and midline shift: patients with tumors larger than 5 cm did not exhibit midline shift more frequently than patients with tumors 5 cm or smaller (chi-squared test = 0.925; p > 0.05).

**Discussion**

The benefits of surgical resection in patients with glioblastoma multiforme remain controversial. This debate has been highlighted by the development of stereotactic technology. Using the criteria defined by Burger and coworkers, we were able to establish with a high degree of accuracy the diagnosis of glioblastoma by means of stereotactic biopsy. No patient died as a result of biopsy or had a lower KPS score after the biopsy procedure. This makes the technique superior to the so-called "open biopsy method" in terms of morbidity, mortality, and accuracy.

The considerable inter- and intratumoral variability of cell migration, neovascularization, permeability disturbances, and necrosis formation might be responsible.

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**TABLE 2**

*Distribution of clinical and radiological parameters in 115 patients with glioblastoma multiforme*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Biopsy Group</th>
<th>Resection Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>58</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>age (yrs)</td>
<td>57 (57)</td>
<td>56 (55)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>duration (mos)</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>mean (median)</td>
<td>2 (2)</td>
<td>3 (2)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>standard deviation</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>preop Karnofsky Performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scale score</td>
<td>65 (60)</td>
<td>71 (70)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>tumor location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lt hemisphere</td>
<td>16</td>
<td>12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>rt hemisphere</td>
<td>36*</td>
<td>19</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>lobar</td>
<td>19*</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>midline</td>
<td>44</td>
<td>57</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Three patients with bihemispheric tumor involvement were excluded.

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**Fig. 1.** Graph showing cumulative survival rates of patients with glioblastoma multiforme after biopsy plus irradiation (squares) and after resection plus irradiation (crosses). The median survival time for the biopsy group was 32 weeks versus 39.5 weeks for the resection group (p = 0.08).
for the lack of contingency between tumor size on contrast-enhanced CT and midline shift in our study. This observation requires more systematic analysis.\textsuperscript{23, 24}

**Prognostic Parameters**

The results of the multivariate analysis, in accordance with findings obtained by other authors, confirm the significance of the patient’s age as a determinant of survival time.\textsuperscript{5, 9} The KPS score was not as important as age in predicting length of survival. Although the performance status was an important factor in univariate analysis, it was confounded by patient age and clinical symptoms in multivariate analysis. Coffey, et al.,\textsuperscript{11} reported similar results; in contrast, however, we did not find a significantly shorter survival time in patients with midline tumors. This might result from the fact that their series included patients with infratentorial glioblastomas, which are known to have a poor prognosis. In the resection group, tumor location had no effect on length of survival. The low incidence of morbidity and mortality after surgical resection, with comparable results in eloquent and noneloquent areas, clearly demonstrates the progress made in microsurgical procedures for gliomas.\textsuperscript{10-12, 17}

**Value of Cytoreductive Surgery**

The aim of the study was to conduct a retrospective comparison of two different treatment strategies (biopsy and radiotherapy vs. surgery and radiotherapy) during a comparable time period, using survival time as the primary endpoint. The comparability and homogeneity of the groups examined, however, were limited by “selection bias.” All of the biopsy patients were judged to have inoperable lesions because of the size and location of the tumors. Only these patients harbored midline tumors, and these patients more often had tumors in the left hemisphere as well as a lower preoperative KPS score than those in the resection group. But there was homogeneity in regard to patient age and the administered course of radiotherapy. Patients who did not receive a conventionally fractionated radiotherapy to a total dose of 50 to 60 Gy were excluded from this study. The comparability of these most important variables was the basis of this study.\textsuperscript{36}

The multivariate analysis of the biopsy and resection groups in our study did not determine any prognostic value of surgery. The median survival time for the resection group was longer than that for the biopsy group, but the difference was not significant. This result was confirmed in the univariate and multivariate regression model. The survival times for the resection group corresponded to the results of larger series reported in the literature with very low morbidity and mortality.\textsuperscript{21, 27, 36} Coffey, et al.,\textsuperscript{11} in particular, published similar results after stereotactic biopsy and radiation therapy, although their study did not include comparisons to a control group. They found a median survival time of 46 weeks in 16 patients with glioblastomas, with no patient presenting with midline shift. The comparison of the survival rates after 26 weeks (chi-squared test = 1.022, \( p > 0.05 \)) and after 1 year (chi-squared test = 0.051, \( p > 0.05 \)) between our series and that of Coffey, et al.,\textsuperscript{11} yields no significant difference.

Reports on the cytoreductive effect of radical surgery are based mostly on the shorter survival times found after subtotal tumor removal, partial resection, or biopsy. The selection bias is usually not taken into account, and no study included a control group.\textsuperscript{10, 18, 33-35, 38, 39} The extent of tumor removal as judged by the surgeon represents a problematic issue,\textsuperscript{26} and postoperative contrast-enhanced CT scans are of little help in estimating the extent of tumor removal, since glioblastomas infiltrate beyond the area of CT contrast enhancement.\textsuperscript{1, 2, 8, 20, 23, 30} In our series, subtotal or partial resection was accomplished in eight patients according to the surgeon; the median survival time of this very small group was 40 weeks. We found no objective differences in the postoperative clinical course between these patients and those undergoing “radical” tumor removal.

The comparable survival times of patients undergoing biopsy and subsequent irradiation and those having tumor resection plus irradiation in a comparable time period raise serious doubt as to the concept of treating glioblastomas with cytoreductive surgery. Radiotherapy is the most effective treatment today for patients with glioblastomas.\textsuperscript{37} Beyond that, there were no significant differences in the KPS scores determined after the end of radiation therapy. Thus, the increased KPS score often observed immediately after tumor resection did not represent lasting clinical superiority with regard to the biopsy group. The most important task of the operation is to eliminate large space-occupying lesions and to remove the neovascularized areas. Clearly, this could be obtained with aggressive surgery. This was confirmed by our study; patients with midline shift were impaired more often during the course of the primary radiotherapy. Otherwise, midline shift was not an important variable in the surgery group. With regard to the lack of cytoreductive surgery in our study, an operation should not be performed in every case; patients with small tumors without midline shift could receive primary radiotherapy only. This hypothesis requires further investigation in the framework of a prospective randomized study.

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