The Role of Tumor Resection in the Treatment of Glioblastoma Multiforme in Adults

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BACKGROUND. The therapeutic impact of tumor resection is poorly defined. Therefore the current study was conducted.

METHODS. A retrospective, 2-institutional study was conducted (1991–1994) to compare the treatment results of stereotactic biopsy plus radiation therapy (99 patients; tumor dose: 60 gray [Gy]) with those of surgical resection plus radiation therapy (126 patients; tumor dose: 60 Gy). Only adult patients with supratentorial, lobar located, de novo glioblastoma were included. Survival time was analyzed with the Kaplan–Meier method. Prognostic factors were obtained from the multivariate Cox proportional hazards model.

RESULTS. Patients were categorized in the Radiation Therapy Oncology Group (RTOG) Classes IV (46 patients), V (157 patients), and VI (22 patients). The resection group and the biopsy group did not differ in terms of age, pretreatment Karnofsky performance status KPS), gender, duration of symptoms, presenting symptoms, tumor location, tumor size, and the frequency of midline shift. Patients in the biopsy group more often were found to have left-sided tumors ($P < 0.001$). Transient perioperative morbidity and mortality rates were 1% and 1%, respectively, in the biopsy group and 5% and 1.6%, respectively, in the resection group ($P > 0.05$). The median survival time was 37 weeks for the resection group and 33 weeks for the biopsy group. The difference was not statistically significant ($P = 0.09$). The most favorable pretreatment prognostic factor was patient age < 60 years ($P < 0.01$). Tumor resection was highly effective in patients with midline shift ($P < 0.01$). In patients without midline shift radiation therapy alone was found to be as effective as tumor resection plus radiation therapy ($P = 0.5$). Patients with midline shift were more likely to have a worse KPS during the course of primary radiation therapy ($P < 0.05$).

CONCLUSIONS. For RTOG Classes IV–VI patients with moderate mass effect of the tumor, radiation therapy alone is a rational treatment strategy. Tumor resection should be performed in patients with pretreatment midline shift whenever possible.

The therapeutic relevance of tumor resection plus radiation therapy compared with radiation therapy alone (after stereotactic biopsy) is poorly defined.[1,2] No prospective, randomized study has been performed. Retrospective studies have produced divergent results.[2–13] Uncontrolled treatment decisions in favor of stereotactic biopsy or open surgery are one major obstacle for proper evaluation of retrospective data; patients receiving stereotactic biopsy usually were older, had an unfavorable pretreatment Karnofsky performance status (KPS), and suffered more often from deep-seated tumors, which may account for a worse outcome.[7–9,14,15] All studies so far have

focused on overall survival rates;[2–13] no study has checked for correlations between pretreatment factors and the efficacy of surgery and/or radiation therapy. The current two-institutional retrospective study (1991–1994) was conducted taking into consideration these ongoing uncertainties: 1) A homogeneous cohort of patients was evaluated, and only adult patients with a lobar located, supratentorial, de novo glioblastoma were included; and 2) correlations between pretreatment factors and the efficacy of surgery were checked and considered in the final prognostic model, if necessary. Stereotactic biopsy was used as a valuable alternative procedure to tumor resection in the Department of Stereotactic Neurosurgery, University, Freiburg; otherwise, tumor resection was the treatment of choice in the Department of General Neurosurgery, University, Freiburg. To the authors' knowledge, this is the first study that compares treatment results from patients who underwent tumor resection and radiation therapy with results from patients who underwent radiation therapy alone (after stereotactic biopsy) for a cohort of patients that was homogeneous regarding all known pretreatment factors and the applied radiotherapeutic treatment.

MATERIALS AND METHODS

The histopathologic diagnosis of glioblastoma was established according to the criteria of the World Health Organization (WHO).[16] A histopathologic review was performed for every patient. To make the patient population as homogeneous as possible, patients 1) with a history of a previously documented low-grade glioma, 2) with a reoperation because of a tumor recurrence, 3) with nonlobar (deep seated) tumors, and 4) with an applied multimodality treatment (that is, additional interstitial implant therapy and/or chemotherapy) were excluded. All patients received limited-field, conventionally fractionated radiation therapy, i.e., 2 grays (Gy) daily, 5 days a week, up to a tumor dose of 60 Gy. Patients with an incomplete course of radiation therapy were excluded. External beam radiation was initiated within 3 weeks after tumor resection and 1 week after stereotactic biopsy, including the tumor and a 2–3 cm margin of surrounding tissue. A macroscopic tumor resection $\geq$ 95%, as estimated by the neurosurgeon, was classified as complete resection; otherwise, surgery was scored as partial resection. Early postoperative contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) scan imaging for evaluation of residual tumor was not performed. Steroids were given in all cases before and after surgery and during the course of irradiation as well. Treatment decisions in favor of surgery or stereotactic biopsy were made independently in the Departments of Stereotactic and General Neurosurgery, University, Freiburg.

Biopsy Group

Between 1991 and 1994, 100 adult patients with a supratentorial, lobar located, de-novo glioblastoma underwent CT-guided stereotactic biopsy and external beam radiation therapy. The biopsy procedure was performed as described previously using the Riechert–Mundinger ring.[9] Briefly, biopsy specimens were taken from the hyperdense and hypodense areas of the tumor along a predetermined trajectory most representative for the tumor. The diagnosis was based on both intraoperatively performed smear preparations and postoperative examination of the paraffin embedded material. One patient died perioperatively and was excluded from further analysis.

Resection Group

Between 1991 and 1994, 128 adult patients with a lobar located glioblastoma were treated with tumor resection plus external beam radiation therapy. The applied diagnostic and therapeutic procedures complied with today's generally accepted standards using microsurgical techniques. Tumor resection was performed as radically as possible in every single patient. Postoperative follow-up native CT scans were obtained on the day of surgery to rule out a bleeding into the tumor site. Two patients died perioperatively and were excluded from further analysis.

Patient Evaluation

The KPS was used to evaluate patients before treatment, after biopsy or surgery (which was measured 1 day after biopsy and 1 week after tumor resection), and at the end of external beam radiation. When the KPS score remained unchanged or was better than the preoperative findings, this was referred to as stabilized or improved status. Otherwise, status was defined as deteriorated.

Statistical Methods

The reference point for survival was the date of the surgical procedure. The length of survival was calculated with the Kaplan–Meier method.[17] Patients who underwent tumor resection were considered as a single surgical group, and their period of survival was compared with that of patients who underwent biopsy using the log-rank statistic. Further grouping by the extent of resection (partial vs. complete) was not performed in the final prognostic model. The Cox regression analysis was used to identify prognostic factors.[18] The variables used for univariate and multivariate analyses were dichotomized. In the prognostic model,

the importance of each covariate was tested first univariately. Second, all variables were fitted together (full model). The "best" model contained only variables associated with length of survival after the adjustment for the effects of the other variables in the full model. The correlation between prognostic (patient, tumor, and treatment related) factors was analyzed using the chi-square statistic. For evaluation of the pretreatment mass effect of the tumor, the covariate midline shift was used. Any shift of the midline ≥ 5 mm was defined as midline shift. Evaluation of pretreatment CT/MRI-scans was performed independently by the attending neuroradiologist (A.B.). An initial (explorative) data analysis of each treatment group was performed to check for asymmetrical or selective effects of pretreatment prognostic factors; it could be shown that midline shift was prognostically unfavorable in the biopsy group ($P < 0.01$) but not in the resection group. Therefore, patients in the biopsy group with and without midline shift were compared separately with all patients in the surgery group to check for correlations between midline shift and the efficacy of surgery and/or radiation therapy. Alternatively, a separate analysis of all patients with and without midline shift was performed to test the validity of the created prognostic model. Comparison of alternative models was performed by computing the maximized likelihood. The following covariates were entered in the final prognostic model; patient age at resection or biopsy (<60 years vs. ≥60 years), KPS (≥70 vs. <70), gender (male vs. female), duration of disease before resection or biopsy (≤4 weeks vs. >4 weeks), symptom at presentation (presence of seizures vs. otherwise), tumor size (greatest dimension of the mostly hypodense [hypointense] central tumor part plus the surrounding hyperdense [hyperintense] part, as defined by contrast-enhanced CT/MRI investigation; ≤4 cm vs. >4 cm), tumor location (frontal vs. otherwise), tumor side (left vs. right), and prescribed treatment (resection [all patients] vs. biopsy [patients without midline shift] and resection [all patients] vs. biopsy [patients with midline shift]).

RESULTS

Treatment groups did not differ in terms of age, KPS, gender, duration of symptoms, symptoms at presentation, tumor size, tumor location, the frequency of midline shift, or the applied tumor dose. Right-sided tumors were found significantly less often in the biopsy group ($P < 0.001$) (Table 1). At the time of data analysis, all patients had died. Transient perioperative morbidity and mortality rates were 1% and 1% in the biopsy group and 5,5% and 1.6% in the resection group, respectively. The difference was not statistically significant ($P > 0.05$). There was complete recovery in all patients in the biopsy group and of the resection group regarding the specific complication. According to the Radiation Therapy Oncology Group (RTOG) prognostic classes (Table 2), the patients in this series fall into Class IV (46 patients; 27.6%), Class V (157 patients, 57.8%), and Class VI (22 patients; 9.8%).15

TABLE 1
Distribution of Pretreatment Clinical and Radiologic Parameters

Parameter	Biopsy group (99 patients)	Resection group (126 patients)	*P* value
Mean age (yrs) (median) ± SD	58 (59) ± 9	57 (57.5) ± 10	0.7
Mean KPS (median) ± SD	70 (70) ± 12	72 (70) ± 11	0.2
Gender (males/females)	51/48	70/56	0.2
Mean duration of symptoms (weeks) (median) ± SD	8 (8) ± 8	8 (8) ± 7	0.2
Symptom at presentation (seizure/other)	26/73	37/89	0.7
Mean tumor size (mm) (median) ± SD	38 (40) ± 13	43 (40) ± 14	0.3
Tumor location (frontal/other)	23/76	34/92	0.6
Tumor side (left/right)	64/35	49/77	<0.001
Midline shift present (no.)	30	47	0.3

SD: standard deviation; KPS: Karnofsky performance status.

TABLE 2
Prognostic Classification of Patients with Glioblastoma[a]

RTOG class	Criteria
III	GBM, age < 50 yrs, KPS ≥ 90
IV	GBM, age < 50 yrs, KPS < 90; or GBM, age ≥ 50 yrs, KPS ≥ 70, tumor resection, working
V	GBM, age ≥ 50 yrs, KPS ≥ 70, tumor resection, unable to work; or GBM, age ≥ 50 yrs, KPS ≥ 70, biopsy only; or GBM, age ≥ 50 yrs, KPS < 70, normal mental status
VI	GBM, age ≥ 50 yrs, KPS < 70, abnormal mental status

RTOG: Radiation Therapy Oncology Group; GBM: glioblastoma; KPS: Karnofsky performance status.
[a] Based on Curran et al.[15]

Prognostic Factors and Length of Survival

Univariate and multivariate analyses

Table 3 gives the probability values of the 9 single-variable models, the full model, and the "best" model. Patient age < 60 years ($P < 0.001$) remained the most important favorable pretreatment factor. The KPS was a powerful prognostic factor after univariate analysis. Its influence decreased after inclusion of the covariate age. It was correlated significantly with patient age ($P < 0.01$). Nonsignificant covariates were gender, duration of symptoms, symptom at presentation, tumor

TABLE 3
Probability Values for the Variables Considered in the Cox Proportional Hazards Model in 225 Patients with Glioblastoma

Variable	One variable model *P* value	Full model *P* value	"Best" model *P* value	Risk ratio
Age	0.0001	0.0001	0.0001	1.8
KPS	0.01	0.12		
Gender	0.5	0.7		
Duration of symptoms	0.2	0.5		
Symptom at presentation	0.08	0.4		
Tumor size	0.2	0.4		
Tumor location	0.3	0.2		
Tumor side	0.3	0.7		
Resection vs. biopsy of tumors with midline shift	0.003	0.002	0.0007	2.0
Resection vs. biopsy of tumors without midline shift	0.5	0.67	0.54	1.1

KPS: Karnofsky performance status.

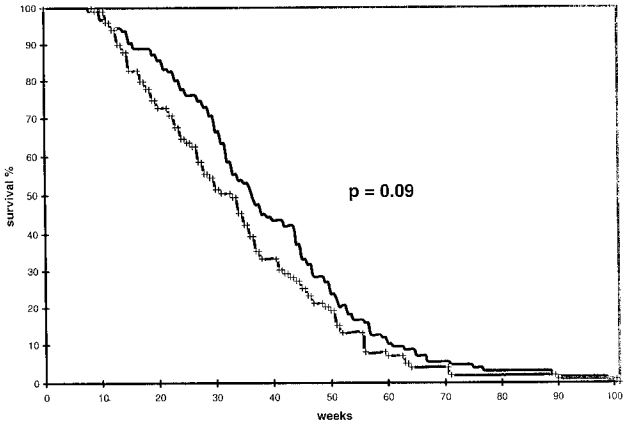

FIGURE 1. Graph showing cumulative survival rates of patients with glioblastoma after tumor resection plus radiation therapy (126 patients; continuous line) and after stereotactic biopsy plus irradiation (99 patients; squares). The median survival rates were 37 weeks and 33 weeks for the resection group and the biopsy group, respectively. The difference was not statistically significant.

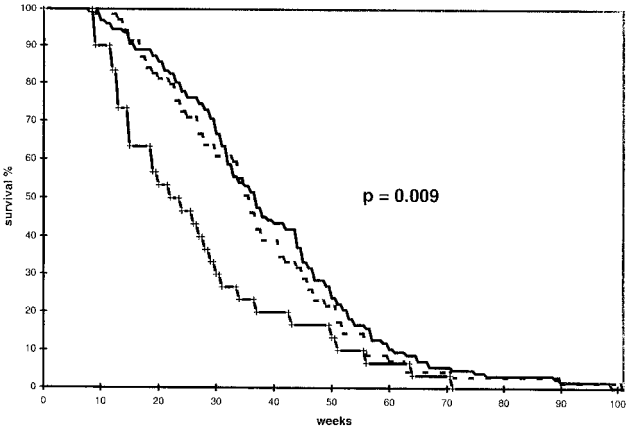

FIGURE 2. Graph showing cumulative survival rates 1) after tumor resection plus radiation therapy (continuous line), 2) after biopsy plus irradiation of tumors without midline shift (broken line), and 3) after biopsy plus irradiation of tumors with midline shift (squares). Those groups comprised 126, 69, and 30 patients, respectively. The median survival rates were 37 weeks, 36 weeks, and 23 weeks, respectively. Survival rates that were as good as those seen after resection plus radiation therapy could be achieved after radiation therapy alone for patients without midline shift. Patients in the biopsy group with pretreatment midline shift did significantly worse.

size, tumor location, and tumor side. Midline shift gained unfavorable influence in the biopsy group but not in the resection group ($P < 0.01$). The frequency of midline shift did not correlate with tumor size. Tumor resection was highly effective in patients with mass effect of the tumor ($P < 0.001$); patients showing pretreatment midline shift had a 2.0 higher risk of death after radiation therapy alone. In patients without midline shift, external beam radiation alone was as effective as tumor resection plus radiation therapy ($P = 0.48$; risk ratio, 1.1). The selective influence of tumor resection could be confirmed by separate analysis of patients with and without midline shift (two-fold higher risk of death for patients of the biopsy group with mass effect of the tumor). The alternative model, however, did not reach a fit as good as the model presented in this study.

Survival rates

The overall median survival times were 37 weeks in the resection group and 33 weeks in the biopsy group (Fig. 1). The difference was not statistically significant ($P = 0.09$). Survival rates for patients in the biopsy group without midline shift (median survival, 36 weeks) were as good as those seen after tumor resection plus radiation therapy (median survival, 37 weeks); 30 patients in the biopsy group who showed a pretreatment midline shift did significantly worse (median survival, 23 weeks; $P < 0.001$) (Fig. 2). The median survival times after complete tumor resection (41 patients) and partial resection (85 patients) were 39 weeks and 36 weeks, respectively. The difference was not statistically significant ($P = 0.5$). According to the RTOG prognostic classes, the median survival rates were 47 weeks (Class IV; 46 patients), 34 weeks (Class V; 157 patients), and 25 weeks (Class VI; 22 patients).

Postoperative Clinical Course

In the resection group, the KPS score at 1 week after surgery was improving (22 patients), stable (97 patients), or deteriorating (7 patients). In the biopsy

group, 2 patients suffered new transient neurologic deficits, and no improvement in the KPS score was noted. The difference between both groups was statistically significant ($P < 0.001$). On completion of radiation therapy, an improvement was seen in 19 (19) patients, stabilization was seen in 79 (52) patients, and was seen in deterioration 28 (28) patients in the resection (biopsy) group, respectively. The difference was not statistically significant ($P > 0.05$). Clinical deterioration during radiation therapy was observed significantly more often for patients in the biopsy group who showed a pretreatment midline shift, i.e., 13 of 30 patients (43%), and 15 of 69 patients (21.7%) without a midline shift deteriorated ($P < 0.05$). In contrast, the risk of clinical deterioration was not influenced by pretreatment mass effect of the tumor in the resection group ($P = 1.0$). The frequency of improvement, stabilization, and deterioration of the KPS after radiation therapy was nearly identical for patients in the resection group and the biopsy group without pretreatment midline shift, i.e., 15.1% (19%), 62.7% (59.4%), and 22.2 (21.7%) in the resection (biopsy) group, respectively.

DISCUSSION

The therapeutic relevance of tumor resection for patients with glioblastoma multiforme is debated.[1–13] No prospective, randomized study has been performed. Available retrospective reports are difficult to interpret due to the heterogeneity of the data.[1–13,15,19,20] Patients receiving incomplete tumor resection or biopsy usually were older, had a lower pretreatment KPS, and suffered more often from deep-seated tumors.[2,3,7–9,11] All studies so far have focused on overall survival. Heterogeneous effects of tumor resection for subgroups of patients have not been reported. Here, the authors present for the first time treatment results after tumor resection plus radiation therapy and radiation therapy alone (after stereotactic biopsy) for a cohort of patients that was homogeneous regarding all known pretreatment prognostic factors and the applied radiotherapeutic regimen. Patients undergoing tumor resection were considered as a single group. Further grouping by the extent of resection (partial vs. complete) was not performed in the final prognostic model, because complex interactions between various degrees of tumor resection and pretreatment factors, e.g., patient age, KPS, tumor location, etc., could not be excluded. Beyond the evaluation of overall treatment effects, the authors checked for correlations between pretreatment prognostic factors and the efficacy of tumor resection and/or radiation therapy to identify subgroups of patients most suitable for surgical treatment. Predominantly RTOG Class IV and V patients were addressed.[15] Retrospective study results should be regarded cautiously and must be confirmed in the framework of a prospective, randomized study.

Pretreatment Prognostic Factors

The results of the multivariate analysis confirm the favorable influence of patient age < 60 years.[2,7–10,12,13,15,19] The KPS was correlated significantly with patient age, which confounds its influence in the multivariate prognostic model. Explorative data analysis revealed a selective, unfavorable influence of midline shift in the biopsy group. The frequency of pretreatment midline shift did not correlate with tumor size, which might be explained by considerable intertumoral and intratumoral variability of cell migration, neovascularization, permeability disturbances, and necrosis formation in patients with glioblastoma multiforme.[20,21]

Efficacy of Cytoreductive Surgery and Mass Effect of the Tumor

Representative treatment results could be achieved in this study. Calculated survival rates were nearly identical to those reported by Curran et al., who have reanalyzed the results of the three RTOG protocols that included 1578 patients.[15] The median survival for patients with RTOG Class IV, V, and VI disease was 44 weeks, 36 weeks, and 18 weeks in the Curran et al. study and 47 weeks, 34 weeks, and 25 weeks in the current report, respectively. Eighty percent of the patients who were reanalyzed by Curran et al. underwent open tumor resection, 100% underwent radiation therapy, and 84% underwent nitrosourea chemotherapy. In contrast, only 56% of the patients in the current study underwent tumor resection, 100% underwent radiation therapy, and no patients underwent chemotherapy. The comparability of the treatment results confirms the role of radiation therapy as the most important therapeutic modality and questions the efficacy of chemotherapy for patients with an intermediate or poor prognosis.

The therapeutic impact of tumor resection was complex in the current study; although overall the median survival time after tumor resection plus radiation therapy was not significantly longer than after radiation therapy alone, a powerful influence of tumor resection was detected for selected patients with significant mass effect of the tumor. Patients showing midline shift did significantly better after tumor resection than after biopsy. Otherwise, in the case of moderate mass effect of the tumor (no midline shift), external beam radiation alone (after stereotactic biopsy) was as effective as open surgery plus radiation therapy. The somewhat selective influence of tumor resection was based on 30 patients in the biopsy group who showed a pretreatment midline shift and also could be

confirmed by separate analysis of patients with and without midline shift, which supports the validity of the created prognostic model. It was concluded that stereotactic biopsy in combination with external beam radiation is a rational treatment strategy in the case of moderate mass effect of the tumor. Microsurgical tumor resection is strongly recommended for patients with midline shift. The obtained results should not be extrapolated to all patients with glioblastoma multiforme. A selected patient population with an intermediate or poor prognosis according to the criteria of Curran et al.[15] was addressed. The therapeutic impact of tumor resection for RTOG Class III patients is unknown and could not be analyzed.

The results of the current study demonstrate that the exclusive focus on overall survival after open surgery and/or radiation therapy easily may obscure the favorable effects of surgery for selected patients. The complex therapeutic impact of surgery was not defined adequately in terms of overall effects of the therapy. Overlooking the correlation between midline shift and the efficacy of the therapy would have led to a serious underestimation of the prognostic influence of tumor resection. Given the heterogeneity of patient, tumor, and treatment related data in numerous retrospective reports and the inadequate check for correlations between pretreatment factors and the efficacy of the therapy, it is not surprising that there is no consensus about the effectiveness of complete tumor resection, incomplete resection, or stereotactic biopsy in the literature.[1–13] For example, patients who underwent incomplete tumor resection had a 6.6 greater risk of death compared with those who underwent complete tumor removal in the study by Albert et al.[3] In contrast, Kowalcuk et al.[2] did not find any favorable influence of gross total tumor resection. Both studies "objectively" evaluated residual tumor using early postoperative CT or MRI scan investigation. Nearly identical survival rates after complete and partial tumor resection were found in the current study, which was in accordance with the data of Simpson et al.[10] but not with those of Winger et al.[12] Subjective (intraoperative) evaluation of residual tumor was performed in those studies. Devaux et al.[8] have reported significantly worse results after stereotactic biopsy than after tumor resection. Kreth et al.,[9] however, have described comparable survival rates after tumor resection and stereotactic biopsy. All of these studies have analyzed a small sample size, often did not consider WHO Grade III and Grade IV tumors separately, have applied uncontrolled surgical and adjuvant treatment concepts, and focused only on overall effects of the treatment.[2,3,8–10,12] Both "objective" and "subjective" evaluation of residual tumor has led to divergent conclusions in the literature regarding the efficacy of open surgery. In the current study data, heterogeneity was minimized. Further grouping by the extent of resection was avoided in the final prognostic model. Ironically, heterogeneous treatment effects of tumor resection and/or radiation therapy were detected that have not yet been acknowledged. It could be demonstrated that both overestimation and underestimation of the efficacy of tumor resection should be avoided. Sixty-three percent of the patients in the resection group could have been treated by radiation therapy alone as effectively as with surgery plus radiation therapy, and 30% of the patients in the biopsy group would have been better treated with open surgery. Each further study on this topic should consider the correlation between the mass effect of the tumor and the efficacy of tumor resection.

It remains a matter of speculation whether tumor resection is working mainly by creating space (decompressive surgery) or significant removal of tumor cells (cytoreductive surgery).[1,2,9] Even though the data from this study easily may be interpreted as decompressive effects of microsurgery, important cytoreductive effects could not be excluded, e.g., a significant removal of radioresistant (hypoxic) neoplastic cells in patients with severe space-occupying tumors. It appears extremely difficult to distinguish between decompressive and cytoreductive effects of surgery, because surgical intervention accomplishes both of these goals.

Postoperative Clinical Course

Patients showed significantly more often immediate improvement in their KPS after microsurgery, which was in accordance with available data in the literature;[6] the rate of improvement, stabilization, and deterioration, however, became similar in both groups after the completion of radiation therapy. Apparently, most of the longer lasting improvements or stabilization in the KPS could be referred to the efficacy of external beam radiation. Midline shift again gained selective unfavorable influence in the biopsy group; patients showing pretreatment midline shift deteriorated significantly more often during the course of primary radiation therapy. Otherwise, midline shift was not an important variable in the surgery group. The frequency of improvement, stabilization, and deterioration of the KPS was nearly identical for patients in both the resection group and the biopsy group without pretreatment midline shift. Thus, tumor resection is not a prerequisite for improvement of the KPS in every case. Taking into account the relatively long period of time necessary for surgery, including the postoperative period spent in the hospital, it was concluded that radiation therapy alone after stereo-

tactic biopsy provides a valuable alternative treatment option for selected patients with an intermediate or poor prognosis in the case of moderate mass effect of the tumor, particularly with regard to the physical aspects of the quality-of-life paradigm.

CONCLUSIONS

Tumor resection is essential for patients with severe mass effect of the tumor (midline shift). Radiation therapy alone after stereotactic biopsy is a rational treatment strategy for patients with intermediate or poor prognoses without midline shift in terms of both survival and quality of life. Each future study on this topic should consider the interaction between the mass effect of the tumor and the efficacy of tumor resection. These retrospectively obtained results require further investigations in the framework of a prospective, randomized study.

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