Prognostic factors in low grade (WHO grade II) gliomas of the cerebral hemispheres: the role of surgery

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Abstract

***Objective*—To assess the role of surgery on survival of patients with grade II gliomas of the cerebral hemispheres.**

***Methods*—One hundred and thirty one low grade hemispheric gliomas surgically treated (biopsied patients excluded) between 1978 and 1989 were retrospectively reviewed. Thalamic, basal ganglia, callosal, or ventricular location were not considered. All tumours were World Health Organisation (WHO) grade II gliomas: 42 fibrillary and 11 gemistocytic astrocytomas, 49 oligodendrogliomas, and 29 oligoastrocytomas. Patients' ages ranged from 14 to 63 (mean 32·9, median 34) years, Karnofsky performance from 0·50 to 0·90 (mean 80·7, median 80), and postsurgical follow up of the living patients from 24 to 190 (mean 97·02, median 93) months. Postoperative external radiotherapy was performed in 49 cases.**

***Results*—The overall survival probability at five years was 97·1%, at eight years 76·1%, and at 10 years 62·7% (median survival time 144 months). The impact on survival of the following variables was analysed: age (<20, 21–40, and >40 years), Karnofsky score (80–100, 70, ⩽70), histology, tumour extension (T1 <3 cm, T2 3–5 cm, T3 > 5 cm maximum diameter), extent of surgical resection (S1 radical, S2 subtotal <10% residual tumour, S3 partial—10%–50% residual tumour), and radiotherapy (either performed or not). A significant positive association with survival at univariate analysis was found for the age group <20 years (P = 0·003), for total and subtotal surgical resections (S1 and S2; P < 0·001) and for the non-irradiated patients (P = 0·0049), whereas a shorter survival probability was noticed for gemistocytic astrocytomas (P < 0·001) and for tumour extension >5 cm (T3; P = 0·0193). Karnofsky performance did not show any significant association with survival. The most relevant factor affecting survival at the multivariate analysis was the extent of surgical resection, which resulted as the only variable retaining a significant value (P = 0·001, risk factor = 2·20).**

***Conclusions*—The data strongly support the role of a surgical removal as extensive as possible in the treatment of these tumours.**

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The obvious optimal purpose of treatment is to cure the patient by suppressing the disease. This goal is unfortunately very rarely achieved when dealing with cerebral neuroepithelial tumours. In most of these cases it is necessarily limited to offering the longest and best quality survival, without producing or further increasing neurological deficits. Within these limitations, resective surgery is generally regarded as the most fruitful means of treatment, even if in several cases it is the first step of a multimodality management. Even if the tumour cannot be completely eradicated, a substantial reduction of its mass can be achieved, thus enhancing the efficacy of other subsequent treatments, such as radiotherapy or chemotherapy.

For low grade gliomas, however, the utility of surgical resection has been questioned.[1–10] Uncertainties regarding their natural history and the possibility of long survival in untreated cases are at the basis of the controversy. The purpose of the present study was to search for further information on the role of surgery, focusing on World Health Organisation (WHO) grade II gliomas of the cerebral hemispheres.

Material and methods

CLINICAL MATERIAL

One hundred and thirty one low grade supratentorial neuroepithelial tumours operated on between January 1978 and December 1989, out of a series of 274 that were initially reviewed, have been retrospectively analysed. Exclusion criteria from the study were: (*a*) grade I gliomas, such as pilocytic or subependymal giant cell astrocytomas, gangliocytomas, or gangliogliomas and dysembryoplastic neuroepithelial tumours; (*b*) well differentiated gliomas showing even minor anaplastic changes; (*c*) age < 14 years (due to the high peak incidence of grade I gliomas in this period of life); (*d*) thalamic, basal ganglia, callosal, or ventricular location; (*e*) lack of adequate preoperative and postoperative neuroradiological records; (*f*) biopsies or minor surgical resections (< 50% of the preoperatively estimated tumour). Two eligible patients (1·5%) died within 30 days of surgery and were excluded from the analysis.

Table 1 Prognostic factors (series analysed: 131 patients)

	n (%)
Age (y):	
14–20	32 (24·7)
21–40	58 (44·1)
> 40	41 (31·2)
Karnofsky PS:	
80–100	105 (80·5)
70	24 (18·2)
< 70	2 (1·3)
Histology (G):	
Astrocytoma	42 (32·0)
Gemistocytic astrocytoma	11 (8·4)
Oligodendroglioma	49 (37·4)
Oligoastrocytoma	29 (22·2)
Tumour size (T):	
T1 (0–3 cm)	17 (13·0)
T2 (3–5 cm)	78 (59·7)
T3 (> 5 cm)	36 (27·3)
Extent of resection (S):	
S1 (total)	76 (58·4)
S2 (< 10% residual)	31 (23·4)
S3 (partial)	24 (18·2)
Radiotherapy:	
No	82 (62·3)
Yes	49 (37·7)

The end point of the study was the surgical outcome in terms of survival. Survival data were obtained from clinical charts, and were recorded as the time from surgery to death or latest follow up examination. All deaths but one were directly related to the cerebral tumour. Some of the possible factors affecting survival were also evaluated. Among these we selected age and presurgical Karnofsky score as factors related to the patients, histology, and tumour extension as related to the tumour characteristics, and extent of surgical resection and radiotherapy as related to the treament (table 1). Chemotherapy was never used. Patients' ages ranged from 14 to 63 (median 34) years. Age was subdivided into three classes: < 20 years, 21–40 years, and > 40 years. Karnofsky performance ranged from 50 to 90 (median 80). Three groups were considered: 80–100, 70 and < 70. Histology included four tumour types[11]: fibrillary astrocytoma, gemistocytic astrocytoma, oligodendroglioma, and mixed oligoastrocytoma. Tumour extension was estimated presurgically by neuroimaging, considering the zone outlined by contrast enhancement or, in non-enhanced lesions, the extension of the CT hypodensity or MRI T1 weighted hypointensity and prolonged T2 hyperintensity. The presence of cysts and calcifications was also considered. In 17 cases (13%) the information obtained from serial stereotactic biopsies was also used. Three classes were considered on the basis of the maximum tumour diameter: T1 < 3 cm, T2 3–5 cm, and T3 > 5 cm. The extent of surgical resection was estimated by comparing the presurgical and postsurgical CT or MRI (performed on the fifth or sixth postoperative week), integrated with the surgeon's perioperative perception. It was subdivided into three classes: S1, indicating a so-called "radical" resection; S2, for residual tumours with maximum diameter less than 10% of that estimated preoperatively, and S3, indicating a partial resection with residual tumour diameter between 10% and 50% of the presurgical diameter. No homogeneous criteria were used to indicate radiotherapy; this varied with the opinion of the surgeon and the radiotherapist referred to; it was performed on 49 patients, in 29 (59·2%) immediately after surgery, and in the remaining 20 (40·8%) at tumour regrowth or progression. A telecobalt unit or a linear accelerator were used to deliver 50–60 Gy target dose in daily fractions of 1·8 Gy, five fractions a week.

The period of clinical observation after surgery ranged from 48 to 192 months. The mean follow up of the living patients was 97·02 (SD 52·81) months (median 93 months, range 24–190 months). No patient of this series was lost to follow up.

STATISTICAL ANALYSIS

Survival estimates were computed according to the Kaplan-Meyer product-limit method[12] and differences in survival were compared with the log rank test for censored data.[13,14] A proportional hazard regression analysis (Cox model)[15] was used to determine the effect of different variables on survival (stepwise selection: enter limit at $P < 0·1$, remove limit at $P > 0·15$). Simple linear regression with the computation of the Pearson's ρ correlation coefficient and t test to determine the equation significance was used to check possible correlation between variables. A paired t test was used to compare continuous variables.

Results

SURGICAL OUTCOME

Overall survival—Median survival time of the whole series was 144 months (fig 1), with a survival probability of 97·1%, 76·1%, and 62·7% at five, eight, and 10 years respectively (censored 71·43%).

Karnofsky performance status—No significant difference was found between preoperative and postoperative Karnofsky score ($P = 0·083$, paired t test). No change was seen in 66 cases (50·6%), an improvement in 50 patients (37·7%), and a decrease in 15 (11·7%).

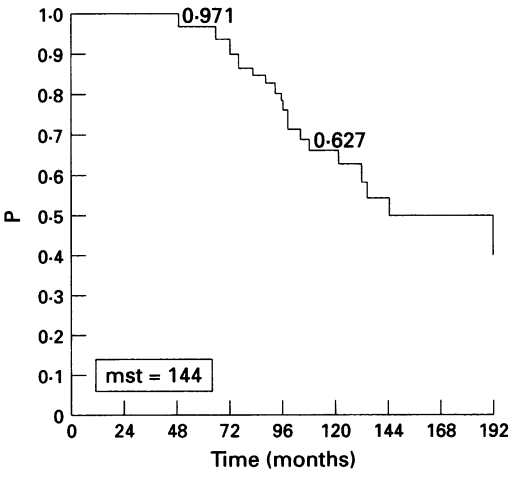

Figure 1 Overall cumulative survival rates for the 131 patients with low grade hemispheric gliomas. mst = Median survival time.

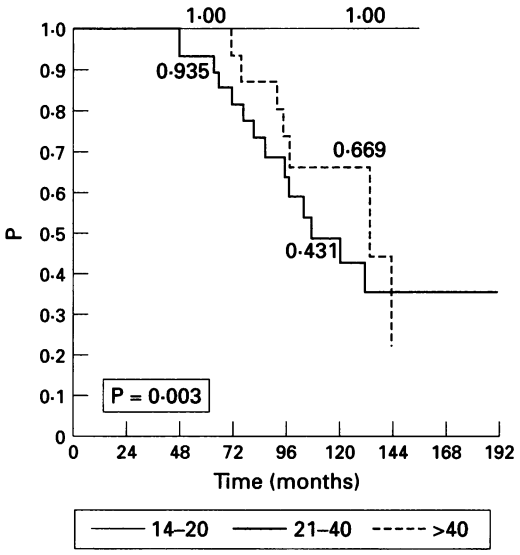

Figure 2 Cumulative survival rates stratified by age (14–20 y, 21–40 y, > 40 y).

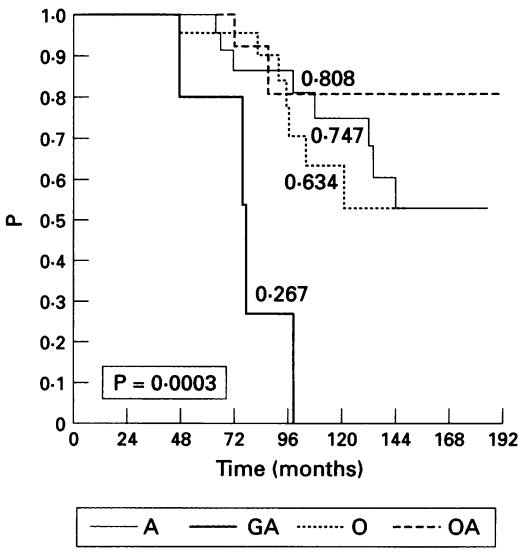

Figure 4 Cumulative survival rates stratified by histology. A = Fibrillary astrocytoma; GA = gemistocytic astrocytoma; O = oligodendroglioma; OA = oligoastrocytoma.

PROGNOSTIC FACTORS

Patient related factors

Age—A significant relation with survival was found, the patients under 20 years (all censored) surviving longer than the older ones (P = 0·003; median survival time not reached; fig 2).

Karnofsky status—No significant association of both the presurgical and postsurgical Karnofsky score with survival was found in our series (P = 0·8187 and P = 0·0966 respectively; fig 3A and B).

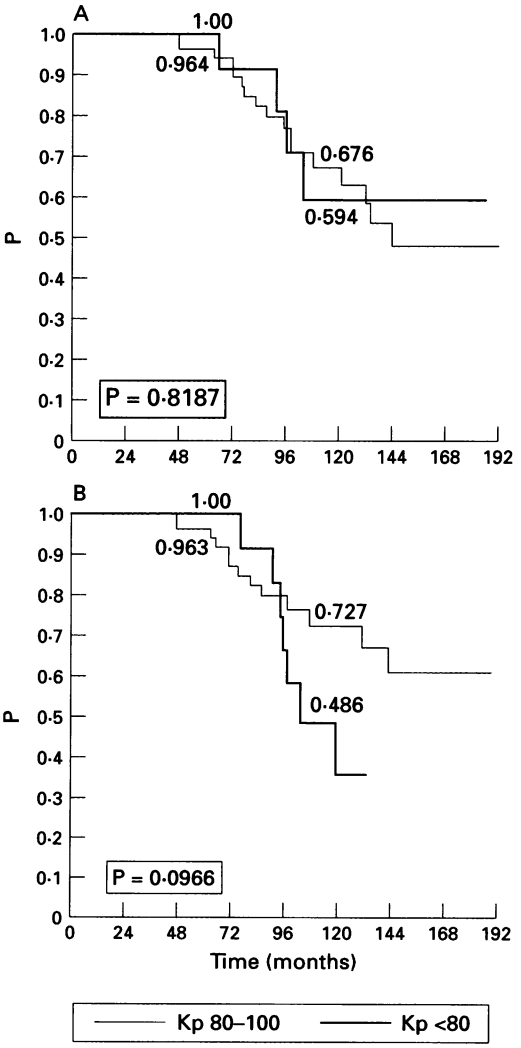

Figure 3 Cumulative survival rates stratified by preoperative (A) and postoperative (B) Karnofsky performance (Kp 80–100, Kp < 80).

Tumour related factors

Histology—Figure 4 shows the relation between tumour histology and survival. Survival curves showed a highly significant difference between the gemistocytic astrocytomas and all the other three histological types (P < 0·001), the first being associated with a lower survival probability (median survival time 77 months, censored 33·3%). No significant differences were found among the other three (P = 0·271).

Tumour size—No significant differences in survival were found by comparing simultaneously the three groups (P = 0·14). A significant difference became apparent (P = 0·0193) when considering the group with tumour diameter > 5 cm (T3; median survival time 121 months, censored 52·2%; fig 5) versus the two

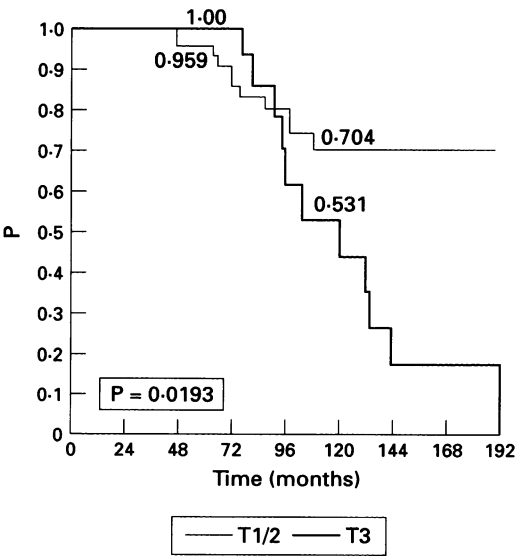

Figure 5 Cumulative survival rates stratified by tumour size. T1/2 = < 5 cm; T3 = > 5 cm.

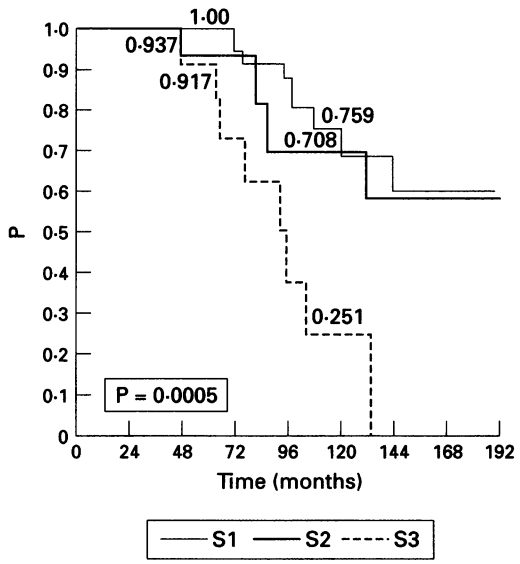

Figure 6 Cumulative survival rates stratified by extent of surgical resection. S1 = Total resection; S2 = subtotal resection with residual tumour < 10%; S3 = partial resection.

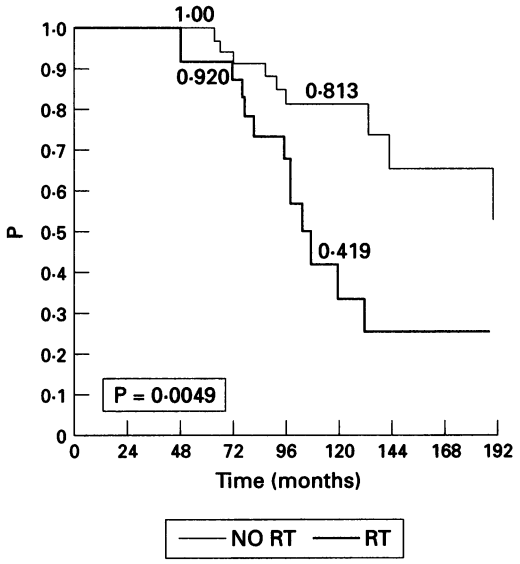

Figure 7 Cumulative survival rates stratified by radiotherapy. NO RT = Not performed; RT = performed.

smaller classes grouped together (T1 + T2; median survival time not reached, censored 79·6%).

Treatment related factors

Extent of surgical resection—The association of the extent of tumour removal with the survival probability was highly significant (P < 0·001; fig 6). Significance was retained when comparing the subtotal (S2) and partial (S3) resection groups (P = 0·005). By contrast, it was lost when comparing radical and subtotal resections (P = 0·319). Longer survival probabilities were found in the S1 group (mean survival time not reached, censored 80%); shorter survivals were found for partial tumour removals (S3 group: median survival time 96 months, censored 42·9%).

Postsurgical radiotherapy—As illustrated in fig 7 a significant difference appeared in the late part of the survival curves. It indicates a surprising better outcome in the non-irradiated patients (P = 0·0049). However, these differences between the survival of the irradiated (mean survival time not reached, censored 81·6%) and non-irradiated patients (mean survival time 108 months, censored 53·4%) disappear if the gemistocytic astrocytomas (all of which were irradiated) are excluded (P = 0·346).

Multivariate analysis

Four variables, all significant in the univariate analysis, were selected to test the strength of their association with survival and to assess their relative prognostic relevance: age, tumour extension (T), extent of surgical resection (S), and histology (G). They were submitted to the Cox proportional hazard model utilising a stepwise procedure to generate the "best" model (table 2). At the final step only the extent of surgical resection retained a significant value (P = 0·001) with a relative risk factor of 2·20, indicating a "hazard rate" of dying 2·2-fold higher for partial resections than for total or subtotal tumour removals. Accordingly, the risk of dying for the two classes (S1 and S2) was estimated to be 54·69% lower than that of the group of partial resection (S3) (coefficient: −0·7916, proportionality factor: 0·4531).

Linear regression analysis

Presurgical tumour extension (variable T) and extent of surgical resection (variable S) were strongly correlated (P = 0·0001); specifically, the smaller the tumour the higher the probability of a radical resection (r = 0·43).

A significant negative correlation was also found between the variable S and the postoperative Karnofsky score (r = −0·3123, P = 0·006), indicating that the more radical the surgical resection the higher is the probability of a better Karnofsky score.

Table 2 Summary of univariate and multivariate analysis

Variable	Individual one variable model (P value)	Full Cox model (P value)	Best Cox model (P value)	(Risk factor)
Age	0·0030	0·0347		
Karnofsky	0·8187	*		
Histology (G)	0·0003	0·9740		
Tumour size (T)	0·0193	0·0273		
Extent of resection (S)	0·0005	0·0012	0·001	2·2069
Radiotherapy	0·0049	†		

*Not evaluated because not significant.
†Not evaluated because of lack of homogeneity of the observations within the group.

Discussion

The duration of survival after resective surgery is higher in our series than in previous reports.[1 4 5–7 9 10 16–29] External radiotherapy, which was used in 37·7% of cases, did not favour survival. Many reasons may account for the longer survival in our patients. Firstly, the comparison among different series is difficult, and probably scarcely useful on account of different criteria of patient inclusion and of tumour categorisation. Secondly, our series is limited to cases mostly treated in the 1980s—that is, when stereotactic biopsy and CT were available for all and MRI for most patients. A comparison of the surgical outcome of the published series dealing with patients treated before the advent of modern neuroimag-

ing[1 6 16 19 20 28 29] with that obtained in the CT and MRI era[4 5 9 10 18 22 25] supports this view. It is likely that both early diagnosis and refinement of the surgical technique contributed to this improvement. Thirdly, all our grade II cases showing even a minor focus of anaplasia were excluded. Fourthly, biopsy was not considered, because of its obvious diagnostic, but not therapeutic purpose.

The age of the patient at the time of surgery, the tumour histology (G), and extension (T), as well as the extent of surgical resection of the tumour were the most significant factors affecting survival in the univariate analysis of our series of grade II hemispheric gliomas. The multivariate analysis showed that the extent of tumour resection (S) was overwhelming, being the only variable retaining a significant value. The presurgical and postsurgical performance status, as expressed by the Karnofsky score was not significantly associated with survival. The role of radiotherapy was not clear.

The role of the *extent of surgical resection* in influencing survival of the low grade gliomas was recognised in previous studies,[16-21 23-31 33 36-38] but it was not supported by others.[1-10] To our knowledge, our study is the first one showing it not only as relevant, but as the most relevant factor affecting survival. Its positive value is strengthened by the relatively low early mortality (1·5%) and, above all, by the low incidence (11·6%) and low degree of worsening of neurological status (minimum postoperative Karnofsky score: 0·60), coupled with its improvement in 37·7% of our patients. It has to be remembered that a higher probability of a better score is expected after complete tumour removal, as stressed by the linear regression analysis. Obviously, the finding of the pre-eminent relevance of the tumour resection is valid only within the limits of our research approach. In particular, its value is dependent on the reliability of the criteria followed to estimate it. In the pre-CT era, the only criterion was the surgeon's impression at the time of surgery. Once modern neuroimaging became available, it was realised how fallacious such a criterion may be. The comparison between presurgical and postsurgical CT and, more recently, MRI was therefore investigated.[4 8 9 18 22 23 30 39-41] However, its reliability was questioned, on account on the uncertainties in defining the boundaries of the tumour process.[2 25 30 41] The leading criterion followed by some was the extent of the contrast enhanced volume,[4 18 30 39 40] but this has serious limitations. Firstly, many low grade primary cerebral tumours do not show contrast enhancement. Secondly, it is known that CT hypodensity and T1 weighted MRI hypointensity, as well as MRI T2 hyperintensity may correspond to tumour tissue with a high cellular content; therefore, they should not be ignored. However, they can also indicate oedema around the tumour, with or without tumour cell infiltration.[41] In our experience, based on the analysis of serial specimens provided by 71 stereotactic biopsies of low grade gliomas performed in the same period, a sharp definition of a hypodense CT or hypointense T1 weighted MRI, or hyperintense MRI T2 weighted area is very likely to be related to a tumour zone densely packed with cells.[30 41] The extension of the CT hypodensity or MRI T2 hyperintensity into the gyral white matter favours its oedematous nature. In the 13% of the patients considered here (n = 17), serial stereotactic biopsy gave a relevant contribution to the presurgical classification of the spatial tumour arrangement in the most doubtful cases.[42] The most intriguing finding remains the presence of isolated tumour cells in CT isodense parenchyma.[41] Despite these limitations we think that the integration of the comparison between presurgical and postsurgical neuroimages with the surgeon's perioperative perception provides the most reliable among the available criteria to evaluate the extension of surgical resection of low grade cerebral tumour. The postsurgical CT or MRI have to be performed at least four to six weeks after surgery to avoid or to reduce possible misinterpretations.

For the other factors analysed, our findings confirm previous ones in pointing out the longer survival in younger patients[4 7-10 18 19 22 23 25-27 30-34] and the more aggressive behaviour of the gemistocytic astrocytoma.[2 9 10 35] The influence of preoperative tumour size on survival has not been so far extensively investigated and is still controversial. Previous studies did not find any significant prognostic relevance.[7 19 36] In our series, on the contrary, a significant impact of the variable T on survival stems from the univariate analysis. The usefulness of postsurgical radiotherapy for low grade gliomas is even more controversial.[1 2 6-10 16 19 21 23 25-29 33 34] The criteria that prompted us in to consider radiotherapy in some cases were the documented incompleteness of the resection or the evidence of tumour regrowth or progression. But we have to admit that these criteria, especially the first one, were not rigid, reflecting our uncertainties for what concerns the gemistocytic astrocytomas. The lack of significant association of the presurgical and postsurgical Karnofsky score with survival in our series contrasts with most of the others,[2 18 19 22 24 25 28] although not with all.[4 10] This might be ascribed, at least in part, to the relative uniformity of the Karnofsky score in our patients, more than 95% of them scoring 0·70 to 1 both before and after surgery. The high rate of presurgical Karnofsky score above 0·80 (80·5%) might have been partly responsible for the length of survival in our patients.

The problem of the management of the low grade cerebral gliomas has been considered in many previous studies. The comparison of the early surgical series with the most recent ones shows a progressive lengthening of survival. Several attempts have been made to delineate the factors related to the best result. Our analysis was on selected material, comprising patients harbouring gliomas of WHO grade II and having an hemispheric location. The extent of surgical resection of the tumour, as already pointed out, proved to be the variable

having the most significant association with survival, and the quality of life during survival was satisfactory. The present study was a retrospective analysis and this basic limiting factor prevents the formulation of definitive conclusions. Actually, this is the conclusion common to almost all the papers on the subject sharing the same limiting factor. Prospective and randomised studies have often been advocated. The point is that such an ideal approach to investigate the role of surgery for the low grade gliomas seems hardly practicable. We would be reluctant to deny surgery to patients with grade II cerebral gliomas having a location and a size well suited for resection, even in the absence of a mass effect. On the other hand, should a prospective study be limited to patients harbouring tumours scarcely suitable for surgical removal, the role of surgery would be a priori very low.

To summarise, at the present time the role of surgical treatment of the low grade cerebral gliomas may be inferred only by comparing the duration and quality of life after partial and gross total resection. That presumes that the extent of resection be defined as accurately as possible, and that its association with survival be matched against other variables inherent to the patient, to the tumour, and to the treatment.

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