Response and progression in recurrent malignant glioma¹

Kenneth R. Hess,² Eric T. Wong, Kurt A. Jaeckle, Athanassios P. Kyritsis, Victor A. Levin, Michael D. Prados, and W. K. Alfred Yung

Departments of Neuro-Oncology (E.T.W., K.A.J., A.P.K., V.A.L., W.K.A.Y.) and Biomathematics (K.R.H.), The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030; and the Department of Neurological Surgery, University of California, San Francisco, CA 94143 (M.D.P.)

In this article we report the results of a study of the relationship between response and progression in 375 patients with recurrent glioma enrolled in phase II chemotherapy trials. We reviewed the records of patients from 8 consecutive phase II trials, including 225 patients with recurrent glioblastoma multiforme and 150 with recurrent anaplastic astrocytoma. Median age was 45 years (range, 15–82) and median Karnofsky performance score was 80 (range, 60–100). Forty-one patients (11%) had more than two prior resections and/or more than two prior chemotherapy regimens. Best response was complete ($n = 1$) or partial ($n = 33$) in 34 patients (9%). Median time to response was 14 weeks, and median response duration was 44 weeks. Simon-Makuch estimates for 52-week progression-free survival for patients progression-free at 13 weeks were 48% for response and 28% for nonresponse. When response was treated as a time-dependent covariate in a Cox proportional hazards regression analysis, response was associated with significantly lower failure rates (hazard ratio 0.5; 95% confidence interval 0.3–0.8; $P = 0.0016$). This study showed that response in recurrent glioma is associated with a significant reduction in progression rates.

Neuro-Oncology 1, 282–288, 1999 (Posted to Neuro-Oncology [serial online], Doc. 99-04, September 7, 1999. URL <neuro-oncology.mc.duke.edu>)

The primary purpose of this study was to examine the relationship between response to chemotherapy and subsequent progression in patients with recurrent malignant glioma. We were motivated by a recent paper (Grant et al., 1997) that concluded that there was no relationship between response to chemotherapy and subsequent progression in patients with recurrent glioma. We had recently aggregated data from eight consecutive phase II trials in recurrent glioma (Wong et al., 1999), and we believed that these data could be used in studying the issue. We also wanted to elaborate on appropriate statistical methodology applicable to this problem.

In this study, we use the term “response” to mean best observed response, either complete or partial, as defined below. The major end point of our study is taken to be progression or death, whichever occurs first. Thus, any patients who died without radiographic or clinical evidence of progression were considered to have had progressive disease. For simplicity, we often refer to the end point as failure. The time from study entry to failure (progression or death) is generally referred to as PFS.³ The time from study entry to death is referred to as OS.

Received 14 January 1999, accepted 13 May 1999.

¹This work was supported by National Cancer Institute Grants CA55621, CA62412, and CA62431.

²Address correspondence and reprint requests to Kenneth R. Hess, Ph.D., Department of Biomathematics, Box 237, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030.

³Abbreviations used are as follows: CR, complete response; KPS, Karnofsky Performance Score; OS, overall survival; PFS, progression-free survival; PR, partial response.

Methods

Statistical Methods

Many studies have described the problems with comparing times to failure between responders and nonresponders (Anderson et al., 1985; Anderson et al., 1983; Buyse and Piedbois, 1996; Feuer et al., 1992; Simon and Makuch, 1984; Weiss et al., 1983). The usual but incorrect

Fig. 1. State transition diagram for a three-state model for tumor response and failure. Patients start in state 1 at study entry. Responding patients enter state 2 at the time of response. Patients enter state 3 when they fail (experience disease progression or die).

approach is to compute the time to failure from study entry (i.e., registration/enrollment) for two groups: patients who ultimately respond, and patients who have disease progression or die without responding. This ignores the fact that all patients initially can be considered nonresponders (in the sense that their tumors do not shrink immediately upon first administration of treatment), and patients do not become responders until some time after study entry. This naïve approach incorrectly attributes follow-up obtained prior to response to the “response group” when it was actually acquired while the patients were nonresponders. A better approach is to think of patient states rather than patient groups (Fig. 1). For the purpose of this study, we have three states: the initial state after enrollment (nonresponse, prior to response or failure); the response state; and the failure state (entered upon progression or death). Patients can transition from state 1 to state 2 or from state 1 to state 3. They can also transition from state 2 to state 3. At any given time, patients may be in any one of the three states. Patients in the failure state may have gone there directly from state 1 or may have gone from state 1 to state 2 to state 3.

One valid method for comparing the time-to-failure (PFS) distributions between responders and nonresponders is to pick some time point after enrollment and use patient status at that point to define the two groups for comparison. Patients with failure prior to this point are omitted. This is called the landmark method (Anderson et al., 1983). One drawback to this method is that results will depend on which time point is selected as the landmark. A related method developed by Simon and Makuch (1984) picks a landmark to start the calculation but lets patients transition into and out of the response state after this point. This method is described in detail in the APPENDIX. The Simon-Makuch approach provides generalized Kaplan-Meier curves that are statistically valid for these data. The corresponding failure rates can be computed as rates of transition into the failure state. These rates can be computed as the hazard rates, which describe the instantaneous failure rates among patients remaining at risk for failure. We can compute hazard functions for failure from state 1 (nonresponse) and for failure from state 2 (response). These functions track how the failure rates change over time. The ratio of haz-

ard rates indicates the relative failure rates between states. If the failure rate from state 1 were higher than the failure rate from state 2, this would indicate that response (state 2) is associated with a reduced rate of failure or, stated another way, prolonged failure times. We can use the Cox proportional hazards model (Cox, 1972) to estimate the ratio of the respective hazard functions. Because group membership changes over time, we can model response as a time-dependent covariate in the Cox model (see APPENDIX).

Statistical calculations were performed primarily using S+ (StatSci Division, MathSoft, Seattle, Wash.). The Cox models with time-dependent covariates and effects were analyzed using both S+ and BMDP2L (BMDP Statistical Software, Los Angeles, Calif.). Algorithms for estimating the hazard function and the Simon-Makuch conditional survival function were written in S+. The data graphs were produced with S+.

Patients

Patients were drawn from eight consecutive phase II chemotherapy trials conducted at The University of Texas M.D. Anderson Cancer Center (Wong, 1999). From 1986 to 1995, seven trials using interferon- β ; interferon- β combined with *cis*-retinoic acid; menogaril; carboplatin; and a combination of carboplatin, 5-fluorouracil, and procarbazine were carried out at M.D. Anderson Cancer Center, and one using eflornithine was carried out at M.D. Anderson Cancer Center and at The University of California, San Francisco. Menogaril, carboplatin, 5-fluorouracil, and procarbazine are known cytotoxic drugs, whereas interferon- β , *cis*-retinoic acid, and eflornithine are thought to be cytostatic agents that mediate antitumor effect by blocking cell growth, without effecting cell kill. The respective institutional review boards approved all trials, and informed consent was obtained from each patient or guardian before enrollment.

Patient eligibility and response criteria were similar among the trials. Briefly, patients with histologically identified malignant gliomas at recurrence were eligible for study. All eight studies required evidence of recurrence after prior radiotherapy and all had similar age criteria (age >16) and performance criteria (KPS $\geq$ 60). Although five of the eight studies did not restrict entry on the basis of previous chemotherapy, one trial excluded patients with any previous chemotherapy, and two trials excluded patients with more than one previous chemotherapy regimen.

Patients enrolled in the studies were evaluated by neurological examinations and neuroimaging studies of the brain—contrast-enhanced CT, gadolinium-enhanced MRI, or both, done at 2-month intervals during the first year, at 3-month intervals during the second year, and at 4-month intervals during the third year, or until disease progression. Response to chemotherapy was assessed by radiographic criteria. CR was defined as complete resolution of tumor by neuroimaging studies, with the patient on a stable or decreasing dose of steroid. PR was defined as a decrease in tumor size (the product of 2 diameters) by 50% or greater, with no increase in steroid dosage. Minor response was defined as a decrease in tumor size

Fig. 2. Event chart for the 34 patients with complete or partial response. Each line represents a single patient. Transitions between states are indicated by symbols superimposed on the line at the time of transition. Patients are sorted by time to response.

of <50%, with stable or decreasing steroid dose. Stable disease was defined as <25% change in tumor size, with stable or decreasing steroid dose. Progressive disease was defined as >25% increase in tumor size or development of a new lesion on imaging studies, with stable or increasing steroid dose.

The histologic diagnosis at the time of registration was recurrent glioblastoma multiforme in 225 patients (60%) and recurrent anaplastic astrocytoma in 150 patients (40%). The median age at enrollment was 45 years (range, 15–82 years). Six patients were younger than 20 and five patients were older than 70. The median KPS at enrollment was 80 (range, 60–100). Twenty patients had a KPS of 100 and 14 had a KPS of 60. Two hundred forty-eight patients (66%) had received prior chemotherapy; 92 patients (25%) received at least two prior chemotherapy regimens. The maximum extent of previous surgery was biopsy in 46 patients (12%), partial resection in 194 patients (52%), and gross total resection in 135 patients (36%). One hundred twenty-eight patients (34%) had undergone two prior surgeries, while 27 patients (7%) had undergone more than two prior surgeries. Forty-one patients (11%) had received more than two prior chemotherapy regimens and/or undergone more than two prior surgeries.

Results

Among the 375 patients, 34 (9%) had CR ($n = 1$) or PR ($n = 33$) as their best response. An additional 18 patients (5%) had minor response, and 94 patients (25%) had stable disease as their best response. Three hundred forty-three patients had experienced disease progression

by the end of the study, and another 14 patients died without evidence of progression. Eighteen patients were alive without progression with a median follow-up of 5.1 years (range, 35 weeks to 8.1 years).

Among the 34 patients with CR or PR as their best response, the median time to response was 14 weeks (range, 4–81) with 74% of responses occurring by 26 weeks and 95% of responses occurring by 50 weeks. The median Kaplan-Meier response duration was 44 weeks; 32% of patients had responses lasting at least 2 years. Response durations of <8 weeks were seen in 15% of the responders. Fig. 2 shows an event chart for the 34 patients with CR or PR as their best response. This plot shows the times to response and response durations for each individual patient.

One approach to exploring the data in terms of patient states is to keep track of how many patients are in each state at various times in the study. All patients start in state 1 by definition and end in state 3 unless they are censored due to study termination prior to failure. At 4 weeks after study entry, 335 patients remained in state 1, and one patient was in state 2 (response). At 8 weeks, 188 patients remained in state 1, and six were in response. At 13 weeks, 47 patients remained in state 1, and 16 were in response. At 26 weeks, 19 patients remained in state 1, and 16 were in response. At 52 weeks, five patients remained in state 1, and 18 were in response. The response state is a transient state experienced by only a subset of patients. The maximum number of patients in the CR/PR response state at any one time was 21 patients at 43 weeks.

Fig. 3 shows hazard functions for failure corresponding to states 1 (nonresponse) and 2 (response). The rates for state 1 reached a peak of 0.10 at 10 weeks, while the

Fig. 3. Hazard function estimates for failure for response and nonresponse. These estimates are based on a time-dependent assessment of response that tracked patients' transition into and out of response and into failure. Estimates are from a kernel approach modified for delayed-entry data and with a fixed bandwidth of 10 weeks. Estimates are shown only for times with at least 10 patients at risk. CR, complete response; PR, partial response.

rates for state 2 reached a peak of 0.04 at 18 weeks. The association between response and progression (failure) can be studied by comparing the failure hazard functions for response and nonresponse. Fig. 3 shows that, at least initially, the progression rates were much lower from state 2 than from state 1. Thus response was associated with lower rates of progression. We can model this association with the Cox proportional hazards regression model using response as a binary (irreversible) time-dependent covariate (Buyse and Piedbois, 1996). This analysis yields an estimated hazard ratio of 0.51 (95% confidence interval 0.33–0.80; $P = 0.0016$). Although Fig. 3 indicates that the ratio of the hazard functions is not constant over time, tests for violations of the proportional hazards assumptions (Grambsch and Therneau, 1994; Hess, 1995) were negative. With only 34 responding patients, however, these tests may have lacked adequate statistical power.

Because responders may have a prognostic advantage relative to nonresponders by virtue of their clinical and demographic characteristics, we performed an analysis adjusting for patient age, histology, performance score, and previous treatment. The proportional hazards analysis yielded an adjusted hazard ratio of 0.53 (95% confidence interval 0.34–0.82; $P = 0.0024$). The association between response and progression was consistent across histologies with estimated hazard ratios of 0.57 for glioblastoma multiforme and 0.40 for anaplastic astrocytoma.

Fig. 4 shows the Simon-Makuch PFS plots for response and nonresponse conditioned on 13 weeks. The 52-week PFS was 48% for response and 28% for nonresponse, while the 104-week PFS was 28% for response

and 14% for nonresponse. The Simon-Makuch plots conditioned on 26 weeks were similar, but those for 52 weeks were closer (104-week PFS of 59% and 49% for response and nonresponse, respectively), indicating a transient nature of the effect of response on failure, similar to that suggested by Fig. 3.

Because survival is considered by some to be the best outcome for use in analyzing studies of treatment for malignant glioma (Rajan et al., 1994), we also included an analysis of the effect of response on OS. The issues were exactly the same as with the analysis of PFS, but the end point was changed from progression to death. A proportional hazards analysis yielded an estimated hazard ratio of 0.40 (95% confidence interval 0.25–0.65; $P < 0.0001$).

Discussion

Grant et al. (1997) found no difference in time to progression and OS between responders and nonresponders in 136 patients with recurrent glioma. They used the radiographic response assessed after two courses of chemotherapy as suggested by Macdonald et al. (1990). Because Grant et al. (1997) did not report confidence intervals for their hazard ratio estimates, it is not possible to determine if their study had adequate statistical power. Since they had 53 patients with stable disease and 34 with minor or partial response, it is possible that some (but not all) of their comparisons had sufficient power to detect clinically important associations (e.g., hazard ratios of 2.0 or larger). Furthermore, they performed an

Fig. 4. Simon-Makuch conditional progression-free survival plots for response and nonresponse. The conditioning time was set at 13 weeks, which is close to the median time to response.

incorrect statistical analysis by treating response as a baseline instead of a time-dependent variable, and they did not adjust for confounding, but both of these flaws would bias their estimates in favor of a stronger association. Thus, there is no clear methodological explanation for their negative results.

Our data show a large difference in PFS and OS between responders and nonresponders. The individual studies used for our analysis combined radiographic and clinical response, put no time limits on when the response could occur (a few occurred after 50 weeks), and did not require confirmation on a second evaluation (15% of the CR/PRs lasted <8 weeks). It is not clear to what extent the differences in response criteria could account for the differences in apparent relationships between response and outcome. Eagan and Scott (1983) in a combined analysis of 5 studies in recurrent glioma used a response definition similar to ours (improved neurologic status and definite decrease in tumor size on CT) and found significant associations between response and survival. Significant associations between response and survival have also been reported in advanced colorectal cancer (Graf et al., 1994), advanced prostate cancer (Slack et al., 1980), advanced ovarian cancer (Torri et al., 1992), and advanced breast cancer (A'Hern et al., 1988).

The question as to whether response is associated with improved overall and progression-free survival is important because the use of response as an end point in early phase clinical trials is based in large part on the notion that tumor response is related to patient survival as well as progression-free survival (Leventhal and Wittes, 1988). However, demonstration of significant associations between response and progression and

between response and survival does not, in itself, imply that response is a viable end point for chemotherapy trials in recurrent glioma. Both response and progression suffer from problems with standards for definitions and lack of reliability (Fine, 1994; Macdonald et al., 1990; Perry et al., 1997; Rajan et al., 1994). While response is a traditional end point for phase II trials because tumor shrinkage suggests biologic activity, progression is increasingly being used, especially for cytostatic agents, which do not target tumor shrinkage as a mechanism of action. Survival, while certainly a more reliable end point than response or progression, suffers from potential confounding from differential application of post-progression therapy (provided these therapies were effective).

Acknowledgments

We thank Jesus Rodriguez, Sandra Ictech, and Mary Jo Gleason for help in data collection and Stephanie Deming for editorial assistance.

Appendix

Consider the three patient states shown in Fig. 1. We can represent the transition rates between states in terms of the hazard functions, which describe the instantaneous transition rates among patients remaining at risk for transition. The hazard functions for transition to state 3 are simply the hazard functions for failure. Let $h_{ij}(t)$ be the hazard function for transition from state i to j . One approach to assessing the transitions between states is to

plot the cumulative hazard functions (Feuer et al., 1992; Simon and Makuch, 1984):

$$H_{ij}(t|x) = \int_x^t h_{ij}(y) dy.$$

Because more people are comfortable with survival function estimates, Simon and Makuch (1984) also describe the transformation of the cumulative hazard function to a conditional survival function:

$$S_{ij}(t|x) = \exp[- \int_x^t h_{ij}(y) dy]$$

The Simon-Makuch approach is an improvement over the landmark approach because patients transitioning into response after the conditioning time (x) have their time at risk correctly attributed to the response state after the transition time, while the landmark method would attribute all of the time at risk to nonresponse since the patient had not responded by time x (Feuer et al., 1992). Simon and Makuch (1984) also describe a slightly different formulation of the conditional survival function that is equivalent to the generalized Kaplan-Meier estimate used for left-truncated or delayed-entry data (Bull and Spiegelhalter, 1997; Cnaan and Ryan, 1989; Kaplan and Meier, 1958).

Related to the issue of estimating the distributions of times-to-failure is the issue of analyzing the differences between the distributions. The usual but incorrect approach is similar to the estimation approach outlined above, ignoring the time to response. The times are computed from enrollment, and groups are formed on the basis of whether the patients ultimately respond or not. This is equivalent to treating response as a baseline covariate and leads to a biased assessment because the follow-up time accrued by responding patients prior to their response is attributed to response instead of nonresponse. This bias is sometimes called the time-to-response bias and acts to make the association between response and failure appear stronger than it really is (i.e., it leads to an overestimate of the strength of the association between response and failure). The bias is sometimes characterized as arising because patients need to survive (progression-free) long enough to respond. A better approach for analysis is to treat response as a time-dependent covariate (Buyse and Piedbois, 1996; Feuer et al., 1992). We can do this within the context of a Cox proportional hazards regression model (Cox, 1972; Klein and Moeschberger, 1997).

Let $z(t)$ represent a time-dependent covariate indicating presence in the response state, and let T_R represent the response time (the time of transition between states 1 and 2). Let $z(t) = 0$ for $t < T_R$ and $z(t) = 1$ for $t \geq T_R$. The hazard function for failure can be modeled as $h(t | z(t)) = h_0(t) * \exp(\beta * z(t))$. The hazard function corresponding to state 1 (nonresponse), $h_{13}(t)$, is the one for $z(t) = 0$, and the hazard function for state 2 (response), $h_{23}(t)$, is the one for $z(t) = 1$. The baseline hazard function, $h_0(t)$, corresponds to $h_{13}(t)$, the failure hazard function for nonresponse. The ratio of these hazard functions is a measure of the effect of response on progression:

$$\frac{h_{23}(t)}{h_{13}(t)} = \frac{h(t|t \geq T_R)}{h(t|t < T_R)} = \frac{h(t|z(t) = 1)}{h(t|z(t) = 0)} = \exp(\beta).$$

This approach assumes that the ratio of the hazard functions between response and nonresponse is constant over time. Inspection of the Grambsch-Therneau-Schoenfeld residuals (Grambsch and Therneau, 1994; Hess, 1995) may indicate that β is a function of the time since enrollment. This gives an extended Cox model: $h(t | z(t)) = h_0(t) * \exp(\beta_0 * z(t) + \beta_1 * z(t) * f(t))$ such that the hazard ratio between states 2 and 1 is now $\exp(\beta_0 + \beta_1 * f(t))$, where $f(t)$ is a function of time (Cox, 1972; Klein and Moeschberger, 1997).

A graphical supplement to the Cox model is to compute the hazard functions for failure corresponding to the two paths of failure: with and without first responding (Pepe and Cai, 1993). In other words, we compute the failure hazard for response, $h_{23}(t)$, and the failure hazard for nonresponse, $h_{13}(t)$. The hazard function describes the instantaneous failure rates (rates of transition to state 3) among patients not in the failure state. To compute the failure hazard from state 1, we censor patients when they transition from the initial state (state 1) to the response state (state 2). To estimate the hazard function for the response state, we must allow for delayed entry into the response state. This requires a simple modification to the usual hazard estimation methods (Klein and Moeschberger, 1997).

To compute a smooth, nonparametric estimate of the hazard function, we use a kernel function approach modified for left truncated or delayed entry data (Klein and Moeschberger, 1997; Wand and Jones, 1997). The kernel estimate is essentially a weighted moving average of the data. We selected the amount of smoothing by visual inspection and restricted estimation to times when at least 10 patients were at risk to avoid unduly unstable estimates. Note that because the hazard functions are instantaneous conditional rate functions, we do not need to specify the conditioning time (x) that is required for the corresponding cumulative hazard and survival functions described by Simon and Makuch (1984). Consequently, the appearance of the hazard functions will not depend on our selection of a conditioning time.

References

- A'Hern, R.P., Ebbs, S.R., and Baum M.B. (1988) Does chemotherapy improve survival in advanced breast cancer? A statistical overview. *Br. J. Cancer* **57**, 615–618.
- Anderson, J.R., Cain, K.C., and Gelber, R.D. (1983) Analysis of survival by tumor response. *J. Clin. Oncol.* **1**, 710–719.
- Anderson, J.R., Cain, K.C., Gelber, R.D., and Gelman, R.S. (1985) Analysis and interpretation of the comparison of survival by treatment outcome variables in cancer clinical trials. *Cancer Treat. Rep.* **69**, 1139–1146.
- Bull, K., and Spiegelhalter, D.J. (1997) Survival analysis in observational studies. *Stat. Med.* **16**, 1041–1074.
- Buyse, M., and Piedbois, P. (1996) On the relationship between response to treatment and survival time. *Stat. Med.* **15**, 2797–2812.
- Cnaan, A., and Ryan, L. (1989) Survival analysis in natural history studies of disease. *Stat. Med.* **8**, 1255–1268.
- Cox, D.R. (1972) Regression models and life tables (with discussion). *J. Royal Stat. Soc. B* **74**, 187–220.
- Eagan, R.T., and Scott, M. (1983) Evaluation of prognostic factors in chemotherapy of recurrent brain tumors. *J. Clin. Oncol.* **1**, 38–44.

- Feuer, E.J., Hankey, B.F., Gaynor, J.J., Wesley, M.N., Baker, S.G., and Meyer, J.S. (1992) Graphical representation of survival curves associated with a binary non-reversible time dependent covariate. *Stat. Med.* **11**, 455–474.
- Fine, H.A. (1994) The basis for current treatment recommendations for malignant gliomas. *J. Neurooncol.* **20**, 111–120.
- Graf, W., Pahlman, L., Bergstrom, R., and Glimelius, B. (1994) The relationship between an objective response to chemotherapy and survival in advanced colorectal cancer. *Br. J. Cancer* **70**, 559–563.
- Grambsch, P.M., and Therneau, T.M. (1994) Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* **81**, 515–526.
- Grant, R., Liang, B.C., Slattery, J., Greenberg, H.S., and Junck, L. (1997) Chemotherapy response criteria in malignant glioma. *Neurology* **48**, 1336–1340.
- Hess, K.R. (1995) Graphical methods for assessing violations of the proportional hazards assumptions in Cox regression. *Stat. Med.* **14**, 1707–1723.
- Kaplan, E.L., and Meier, P. (1958) Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* **53**, 457–481.
- Klein, J.P., and Moeschberger, M.L. (1997) *Survival Analysis: Techniques for Censored and Truncated Data*. New York: Springer. pp. 153, 271, 276.
- Leventhal, B.G., and Wittes, R.E. (1988) *Research Methods in Clinical Oncology*. New York: Raven Press. pp. 69–70.
- Macdonald, D.R., Cascino, T.L., Schold, S.C., Jr., and Cairncross, J.G. (1990) Response criteria for phase II studies of supratentorial malignant glioma. *J. Clin. Oncol.* **8**, 1277–1280.
- Pepe, M.S., and Cai, J. (1993) Some graphical displays and marginal regression analyses for recurrent failure times and time dependent covariates (in theory and methods). *J. Am. Stat. Assoc.* **88**, 811–820.
- Perry, J.R., DeAngelis, L.M., Schold, S.C., Jr., Burger, P.C., Brem, H., Brown, M.T., Curran, W.J., Scott, C.B., Prados, M.D., Kaplan, R., and Cairncross, J.G. (1997) Challenges in the design and conduct of phase III brain tumor therapy trials. *Neurology* **49**, 912–917.
- Rajan, B., Ross, G., Lim, C.C., Ashley, S., Goode, D., Traish, D., and Brada, M. (1994) Survival in patients with recurrent glioma as a measure of treatment efficacy: Prognostic factors following nitrosourea chemotherapy. *Eur. J. Cancer* **30A**, 1809–1815.
- Simon, R., and Makuch, R.W. (1984) A non-parametric graphical representation of the relationship between survival and the occurrence of an event: Application to responder versus non-responder bias. *Statist. Med.* **3**, 35–44.
- Slack, N.H., Mittelman, A., Brady, M.F., and Murphy, G.P. (1980) The importance of the stable category for chemotherapy treated patients with advanced and relapsing prostate cancer. *Cancer* **46**, 2393–2402.
- Torri, V., Simon, R., Russek-Cohen, E., Midthune, D., and Friedman, M. (1992) Statistical model to determine the relationship of response and survival in patients with advanced ovarian cancer treated with chemotherapy. *J. Natl. Cancer Inst.* **84**, 407–414.
- Wand, M.P., and Jones, M.C. (1997) *Kernel Smoothing*. Second edition. New York: Chapman and Hall.
- Weiss, G.B., Bunce, H., III, and Hokanson, J.A. (1983) Comparing survival of responders and nonresponders after treatment: A potential source of confusion in interpreting cancer clinical trials. *Control. Clin. Trials* **4**, 43–52.
- Wong, E.T., Hess, K.R., Gleason, M.J., Jaeckle, K.A., Kyritsis, A.P., Prados, M.D., Levin, V.A., and Yung, W.K.A. (1999) Outcomes and prognostic factors in recurrent glioma patients enrolled in phase II clinical trials. *J. Clin. Oncol.* **17**, 2572–2578.