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Challenges in the design and conduct of phase III brain tumor therapy trials

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Twenty years ago a phase III trial by the Brain Tumor Study Group demonstrated that surgery and radiation were better treatment for malignant glioma than surgery alone.[1] Maximal surgical resection and conventional radiotherapy quickly became the standard of care for patients with high-grade glioma. Since then many other treatments, most often cytotoxic drugs,[2] have been added to surgery and radiation, and compared with standard therapy in randomized controlled trials (RCTs). None has unequivocally prolonged tumor control or patient survival.[3] While these failures speak largely to the resilient nature of malignant glioma, certain issues surrounding the initiation and conduct of phase III trials of brain tumor treatment have surfaced in recent years and warrant discussion before the next generation of antiglioma therapies are tested. Some RCTs were based on inconclusive phase II data and may have been initiated prematurely, while others had divergent entry criteria, inadequate control for prognostic factors, and different outcome measures. Moreover, few studies evaluated quality of life (QOL), toxicity, or cost in a comprehensive way and none considered patient preferences for treatment. In this report we describe methods of assessing the results of phase II trials as a means of selecting treatments that most warrant phase III evaluation, and discuss challenges in the design and conduct of RCTs of new therapies for malignant glioma.

When is an RCT warranted? When are the results of a phase II study sufficiently compelling to warrant a randomized trial? Randomized controlled trials are initiated when new treatments are found to have antiglioma activity in phase II evaluation. Phase II trials are of two types: (1) those that measure tumor response and (2) those that measure tumor control. In studies of *response*, treatment is given to patients with visible tumor, and the rate and duration of the response is recorded. In studies of tumor *control*, the effects of therapy on progression-free and overall survival are recorded. Customarily, systemically administered cytotoxic treatments are assessed by measuring response, usually in patients with recurrent tumor, whereas locally directed cytotoxic therapies are evaluated by measuring progression-free and overall survival in patients with either new or recurrent malignant glioma. Phase II trials of both types will continue to be used, although studies of tumor control may predominate as traditional chemotherapies give way to cytostatic compounds that limit growth, invasion, and angiogenesis. The question, "When is an RCT warranted?" can be rephrased as, *What rate or duration of response, or progression-free or overall survival in a phase II trial reliably identifies a promising therapy for malignant glioma?* Today there is no simple answer to this fundamental question, although certain conclusions can be drawn from our collective experience with RCTs.

Phase II studies of the response type are the principal vehicle for the identification of potentially useful cytotoxic therapies for cancer and, historically, predict treatments that may prove helpful therapeutically. Although response per se does not guarantee enhanced tumor control or patient survival, response to a cytotoxic agent is likely an important indicator of antiglioma activity. For malignant astrocytoma and glioblastoma, we do not know what rate or duration of response constitutes a promising result worthy of further study in an RCT, nor is there universal agreement on what degree of tumor reduction constitutes a response, although increasingly the standard is ≥50% decrease in cross-sectional area[4] or volume after controlling for steroid effects on imaging.[5,6] We have learned, however, that cytotoxic chemotherapies such as carmustine (BCNU) with low rates of partial response (<40%) and short durations of response (<1 year) do not appear to prolong tumor control or patient survival when added to surgery and radiation.[2,3] Unlike malignant astrocytic tumors, anaplastic oligodendrogliomas are relatively chemosensitive. The

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drug combination procarbazine, CCNU (lomustine), and vincristine—PCV—induces some complete responses, high rates of partial response (75%), and long durations of response (>1 year).[7] Furthermore, for oligodendroglioma, there is a direct relationship between the degree and duration of response.[8] These data justified an intergroup RCT by the Radiation Therapy Oncology Group (RTOG) evaluating neoadjuvant chemotherapy for anaplastic oligodendroglioma. This study and the trend to "upfront" response assessment in nonirradiated patients with gliomas of all types may clarify the threshold for initiating an RCT based on rates of tumor response.

Phase II studies of the tumor *control* type are common in neuro-oncology. They have been the principal vehicle for assessing many new treatments for malignant glioma, including brachytherapy, stereotactic radiosurgery, photodynamic therapy, intra-arterial chemotherapy, intracavitary chemotherapy by drug-impregnated wafer or Ommaya reservoir, and regional immunotherapy. Studies of the tumor *control* type are necessary because response (and sometimes time to progression) may be impossible to assess accurately after certain intense local cytotoxic therapies because both tumor and treatment effects can have similar clinical and radiologic features. Unfortunately, uncontrolled trials using survival data to judge therapeutic efficacy are vulnerable to selection bias and may give misleading results, as two recent studies have shown. Florell et al.[9] analyzed the survival of patients with malignant glioma judged eligible for brachytherapy, but treated in a conventional fashion, and observed that eligible patients lived significantly longer than ineligible patients (16.6 months versus 9.3 months) and substantially longer than the entire group of unselected patients (16.6 months versus 11.4 months). Patients eligible for brachytherapy had favorable prognostic factors and consequently had good outcomes. Shortly thereafter an RCT by the Brain Tumor Cooperative Group (BTCG) demonstrated that brachytherapy had considerably less impact on patient survival than anticipated from phase II experience.[10] Subsequently, Curran et al.[11] reanalyzed the survival of patients with malignant glioma in the RTOG database and found that five variables (duration of symptoms, presenting neurologic abnormalities, age at diagnosis, tumor grade, and postoperative performance status) defined six patient subgroups with distinct prognoses. Each subset received similar treatment yet their median survivals varied from 4.7 to 58.6 months. This study demonstrated that pretreatment variables influenced survival as much or more than treatment.

Both types of phase II studies are vulnerable to biases that may enhance results, but response is usually indicative of some biological effect whereas progression-free and overall survival may be due entirely to patient selection. Thus, to select therapies for RCTs, methods for detecting bias in phase II studies of the tumor control type are essential.[9] Kirby et al.[12] used a modeling technique to simulate the selection of patients for intra-arterial BCNU, a promising therapy that proved ineffective and toxic in an RCT by the BTCG.[13] They observed that patients treated conventionally but eligible for intra-arterial BCNU, those treated with intra-arterial BCNU in phase II trials, and those randomized to either intra-arterial or intravenous BCNU in the BTCG trial had similar survival times (14.8 months versus 12 to 18 months and 11.2 months versus 14.0 months). Using a database of conventionally treated patients with malignant glioma, Kirby et al.[12] demonstrated that the negative RCT of intra-arterial BCNU may have been predictable, the apparent benefit of intra-arterial treatment a consequence of patient selection. This study suggests that modeling techniques might assist in the interpretation of phase II trials of the tumor *control* type helping to identify therapies that warrant phase III evaluation.

Stereotactic radiosurgery is a promising therapy for patients with small gliomas and good performance status. Loeffler et al.[14,15] treated 69 patients with newly diagnosed glioblastoma multiforme, observing a median survival of 19.7 months. Might this long survival be explained by patient selection? Three groups, relying on databases, reached different conclusions about the need for an RCT. Using the RTOG database, Curran et al.[16] found that patients with small glioblastomas and good function at diagnosis (potentially eligible for radiosurgery), lived significantly longer than other patients (12.5 months versus 10.5 months) and longer than expected, but called for an RCT because radiosurgical patients had much better outcomes (19.7 months versus 12.5 months). Sarkaria et al.[17] observed that patients receiving radiosurgery lived significantly longer than control patients from the RTOG database matched for pretreatment variables and recommended an RCT, but were not certain that control patients had small tumors or were eligible for radiosurgery. Irish et al.[18] used a smaller database of conventionally treated patients to model the selection process for radiosurgery precisely, basing eligibility on postradiation images and performance status. Eligible patients with glioblastoma lived much longer than expected (16.4 months versus 8.8 months). They concluded that an RCT was not yet justified because patient selection explained long survival times in uncontrolled trials. On the strength of phase II data and analyses by Curran et al.[16] and Sarkaria et al.[17] the RTOG initiated an RCT. This trial will clarify the therapeutic value of radiosurgery and perhaps also clarify the predictive value of different methods of phase II data analysis. Modeling techniques will not replace RCTs but may help prioritize new treatments for further study.

Comprehensive databases of unselected, conventionally treated patients with new and recurrent malignant glioma (from which relevant control groups can be culled) are essential to interpret properly uncontrolled trials of novel therapies for glioma. We recommend that resources be identified to develop and maintain these valuable clinical research tools and that no RCT be initiated until investigators demonstrate that progression-free or overall survival in phase II studies of the tumor *control* type substantially exceed those expected for comparably selected patients.

How should an RCT be performed? *Statistical considerations.* Most RCTs examining the treatment of malignant glioma sought a 50% increase in median survival in the experimental versus control arm, yet most had insufficient power to detect a benefit of this magnitude and none was large enough to exclude a 25% increase.[19] A negative trial with adequate power excludes a significant benefit, but one with insufficient power may miss a treatment effect. Indeed, lingering doubts about the value of adjuvant BCNU for malignant glioma can be attributed to

a series of RCTs with insufficient power to detect a modest prolongation of survival. Using standard levels of statistical significance and assuming a median survival of 9.4 months for glioblastoma, 136 patients are required per treatment arm to demonstrate a 50% increase in survival (two-sided $\alpha = 0.05$, $\beta = 0.20$, accrued over 2 years).[20] Most RCTs evaluating adjuvant chemotherapy were this size or smaller. Four hundred eleven patients per treatment arm are required to demonstrate a 25% increase in survival. Reluctance to participate in clinical research and the relative rarity of malignant glioma are significant obstacles to large-scale RCTs, but some therapeutic questions cannot be answered definitively in any other way. To select the appropriate sample size for an RCT, investigators must decide a priori the degree of treatment effect they wish to detect. This implies agreement on the outcome to be measured and consensus on what difference in outcome is important. Oncologists focus on survival, but Naylor and Llewellyn-Thomas[21] have argued that this question should be asked of patients, so their preferences for care are considered in the design of RCTs. Understanding the outcomes and benefits that glioma patients value most is a priority for research in neuro-oncology.

Outcome measures. All outcomes should be stated explicitly and, to avoid bias, analyses should be performed on an intent-to-treat basis. Significant differences noted in valid study group or post hoc analyses should be viewed skeptically, especially if the trial's overall result is negative and the subgroup variables were not prespecified.[22] Uniform treatment at recurrence, standardized terminal care, and a log of losses to follow-up are other desirable (but less practical) design features of RCTs for brain tumor.

There are several possible end points for RCTs evaluating glioma treatment: survival, time to tumor progression (TTP), toxicity of treatment, and QOL.

Survival. Median survival has been the major end point in most RCTs; proportionate survival at 1 or 2 years has been used in some. Survival is an objective outcome and much easier to measure than TTP, toxicity of treatment, or QOL but survival alone may be an insufficient end point for brain tumor therapy trials. For a disease like glioma that threatens intellect, locomotion, and other basic human functions, it could be argued that QOL is a more important measure of successful treatment than survival. Faced with a fatal illness most patients with malignant glioma seem willing to endure temporary side effects in return for prolonged independence and some chance of longer life, but few willingly sacrifice quality for length of life. Moreover, survival results can be misleading at times. Life-prolonging therapy at relapse, if applied unequally in the experimental and control arms of an RCT, can lead to false-positive or negative results and erroneous conclusions. Survival is an important outcome measure in RCTs evaluating glioma therapy, but small differences between study arms, even if statistically significant, must be viewed cautiously, especially when treatment at relapse is not standardized and QOL is not measured.

Time to tumor progression. Time to tumor progression has advantages and shortcomings as an outcome measure in brain tumor therapy trials. It is a direct measure of the efficacy of initial therapy, unaffected by treatment at recurrence, but is often a less objective end point than survival. Usually TTP is based on clinical or imaging criteria, both of which can be measured but have an element of subjectivity and both of which fluctuate with changes in steroid dose.[5,6] RCTs are unlikely to mandate that TTP be verified by reoperation in all patients, although this is common practice at some brain tumor centers. Moreover, TTP may be difficult to assess. Some local therapies cause a necrotizing reaction in the tumor bed that clinically and radiologically is indistinguishable from recurrent glioma. Positron emission tomography and MR spectroscopy may help distinguish tumor from necrosis, but they have limited sensitivity and specificity, and are unavailable outside major centers. Time to tumor progression may be a valuable end point for systemic therapies such as cytotoxic drugs that do not cause a significant, local inflammatory reaction in the brain, but may be an inappropriate end point for trials evaluating intense, locally directed therapies such as radiosurgery, brachytherapy, gene therapy, or intracavitary chemotherapy.

Toxicity of treatment. Scales for assessing acute nonneurologic toxicities are well developed in oncology and invariably included in brain tumor therapy trials. However, brain tumor patients have specific acute and delayed neurologic toxicities that are addressed poorly in all-purpose toxicity scales. New measurements, like time without symptoms and toxicities (TWiST), and QOL and TWiST,[23] evaluate survival, toxicity, and QOL in a single, integrated format that adjusts survival time for time spent with undesirable effects. The traditional RCT outcomes—survival and TTP—are adjusted for time with toxicity using these comprehensive instruments. These methods may be useful in studies of chronic neurologic disorders[24] and general oncology,[23] and particularly applicable to brain tumor therapy trials.[25] We recommend that toxicity of treatment continue to be a secondary end point in RCTs for brain tumor but that new disease-specific and integrated toxicity instruments be developed further.

Quality of life. Several cooperative oncology groups now require that QOL be an outcome measure in all RCTs.[26] Global performance and job status were reported in the first RCT evaluating chemotherapy for malignant glioma published in 1971,[27] but no brain tumor therapy trial has evaluated QOL in a comprehensive fashion. Karnofsky performance status (KPS) is an eligibility criterion for brain tumor therapy trials and an important prognostic factor, but correlates poorly with QOL.[28] Simple, valid reproducible instruments sensitive to changes in the health status of brain tumor patients are being developed. Mackworth et al.[29] generated a brain tumor-specific questionnaire, designed as a supplement to the QLQ-C30 QOL instrument developed by the European Organization for the Research and Treatment of Cancer (EORTC).[30] Recently Weitzner et al.[31] published the Functional Assessment of Cancer Therapy (FACT) brain subscale, a comprehensive, brain tumor-specific QOL instrument that incorporates patient and caregiver input. The original FACT scale,[32] like the EORTC QLQ-C30,[30] was developed by experts as a base module to which disease-specific subscales could be appended. With further validation such scales are likely to become standard for assessing QOL in brain tumor patients. We recommend that QOL be at least a secondary outcome measure in RCTs evaluating the treatment of patients with malignant glioma.

Prognostic factors and stratification. Age, postoperative KPS, and tumor grade are the important determinants of survival for patients with malignant glioma.[9,33] Even distribution of these factors in the arms of an RCT is critical and can be accomplished by pretreatment stratification or post hoc multivariate analysis. Stratification is preferable but, as it may increase the sample size required for an RCT, should be restricted to those variables known to influence outcome. Based on the consistently important influence of age, two strata are recommended: <50 years and ≥50 years. No upper age limit is necessary but children (i.e., <16 or <18 years) should be studied separately. Two strata for KPS are recommended: 50 to 70 and 80 to 100 (alternatively, 50 to 60 and 70 to 100). Stratification on the basis of performance status may not be necessary if eligibility is restricted to patients with a postoperative KPS ≥80. Patients with good performance status are likely to complete the prescribed treatment and are unlikely to die early, but a more inclusive trial (e.g., KPS ≥50) mimics clinical practice and makes it easier to accrue large numbers of patients to RCTs. Patients with lower KPS scores (e.g., 50 to 70) may benefit less from treatment, but the greater power and generalizability of a larger RCT outweigh this concern.[34] In very large studies it may be possible to stratify KPS further (e.g., 50 to 60, 70 to 80, 90 to 100), although this might be handled equally well in a post hoc multivariate analysis. Two strata for pathology are recommended: anaplastic astrocytoma and glioblastoma/gliosarcoma. Given their unique molecular profile[35,36] and response to therapy,[37] we suggest separate RCTs for patients with oligodendroglioma and mixed glioma. Predefined histologic criteria and central review by a single expert or consensus panel are mandatory, especially if nonglioblastoma pathologies are to be included, because misclassification of patients will affect the power of a trial.[38] Unfortunately there is no universally accepted grading scheme for astrocytic neoplasms. The World Health Organization (WHO) method[39] may prevail, however, because it is simple and objective. The WHO scheme was adapted from the St. Anne-Mayo system,[40] which has a 94% interrater correlation.[41]

Extent of resection from the operative note has been an independent determinant of survival in some analyses but not others.[42-44] Ability to resect is influenced by a variety of factors including age, performance status, and tumor location, and is less accurately estimated by surgeons than early postoperative CT or MRI,[45] perhaps explaining why extent of resection has been an inconsistent prognostic factor in retrospective studies and RCTs. Wood et al.[46] observed that tumor burden on postoperative CTs was a more important predictor of survival than degree of resection; and, likewise, Albert et al.[45] noted that postoperative tumor volume on MRI was a more important determinant than either age or performance status. We recommend that RCTs include all patients regardless of degree of resection, but require early postoperative imaging (within 72 hours) to assess residual tumor burden. Post hoc multivariate analysis should suffice to correct imbalances between treatment groups and examine the influence of residual tumor burden on survival and other outcomes. Both the maximal cross-sectional area and volume of contrast-enhancing disease are used to estimate tumor size and are adequate for response assessment. Nevertheless, imaging outcomes require further study of their reliability and predictive value.

Cointervention and concurrent therapy. Nonstudy treatments and cointerventions are difficult to control and may bias the results of an RCT. This is chiefly a problem when survival is the primary outcome measure. Many nonstudy interventions may take place between randomization and death, especially at relapse and during the terminal phase. Treatment options at recurrence range from no active therapy to high-dose steroid treatment with aggressive re-resection and reirradiation. Such therapy may influence survival. For example, Brem et al.[47] demonstrated recently in an RCT that patients with recurrent malignant glioma live longer after reoperation and BCNU polymer implant than after reoperation alone. Management options for terminal care also are numerous, ranging from comfort measures to aggressive treatment with antibiotics, high-dose steroids, and venous thrombosis prophylaxis. (The impact of "aggressive" care is unknown and unlikely to be studied extensively.) Solutions to the problem of cointervention and concurrent therapy are difficult to implement and monitor but ideally include a log of nonstudy drugs and treatments, uniform criteria for intervention at recurrence, and similar application of late-stage therapies across all arms. In the long term, as initial treatment improves and TTP lengthens, cointerventions and concurrent therapies may be less important issues because survival postrecurrence may be a smaller proportion of overall survival than it is currently.

Control arms. Customarily, RCTs test a new intervention against the current standard of care. Whether any therapy beyond maximal resection and conventional radiotherapy should be considered standard treatment for malignant glioma is debatable. The role of adjuvant chemotherapy remains unclear. RCTs have had insufficient power to detect a modest survival benefit confidently. Fine et al.[48] attempted to resolve the issue by meta-analysis, a statistical technique that allows trials with insufficient power or conflicting results to be combined and reanalyzed. They pooled data from 16 selected RCTs of adjuvant chemotherapy and found a 10% increase in the 1-year survival rate with no significant increase in median survival.[48] This finding, while interesting, should not be considered an endorsement of adjuvant chemotherapy for malignant glioma. Meta-analysis, like post hoc subgroup analysis, is a method for generating hypotheses, not testing them.[49] Furthermore, many previous glioma trials lend themselves poorly to this type of analysis because weaknesses in individual RCTs are incorporated into meta-analyses and jeopardize their conclusions.[49,50] Many authors believe that the results of a single, well-designed RCT are more powerful than a meta-analysis, especially for deriving treatment recommendations.[49] As we interpret the evidence, the standard of care for malignant glioma in 1997 is maximal feasible surgical resection and conventional external beam radiotherapy. Adjuvant chemotherapy is a treatment option but is not of unequivocal benefit for any type of malignant glioma. Although some neuro-oncologists use adjuvant PCV chemotherapy routinely for patients with anaplastic astrocytoma, this practice is based largely on a post hoc analysis of an otherwise negative RCT[51] that has not been confirmed in a study designed specifically to address this issue. We recommend a

radiotherapy-only (i.e., no chemotherapy) control arm in RCTs evaluating the initial treatment of malignant glioma. This view is concordant with the design of the intergroup RCT for oligodendroglioma by the RTOG in which PCV followed by radiation is compared to radiation alone.

Increasingly limited resources for clinical research and a series of disappointing RCTs are forcing neuro-oncologists to rethink how new therapies for glioma are evaluated. We can no longer "afford" to misinterpret phase II data, mistaking bias for efficacy; conduct RCTs with insufficient power; omit toxicity and QOL evaluations from brain tumor therapy trials; and ignore patient preferences for treatment or the outcomes they value most in the design of RCTs. Before testing the next generation of glioma therapies, standards for initiating and conducting phase III brain tumor therapy trials are needed. Hopefully the issues raised in this review will move neuro-oncologists a step closer to a standard methodology for RCTs.

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