The role of surgery in the management of supratentorial intermediate and high-grade astrocytomas in adults

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In this analysis, the authors review studies over the last 50 years addressing the association between long-term survival and type of surgical management in adults with supratentorial intermediate or high-grade astrocytomas. Earlier reports are included because they are repeatedly referenced in current works and clearly are an important basis upon which present attitudes are predicated. Because recent work has definitively demonstrated the significance of prognostic variables on outcome, the handling of such factors in studies that investigated survival data according to degree of surgery is emphasized. Study design, experimental methods used, and methods of data analysis are also examined. This analysis shows that there is little justification for dogmatic statements concerning the relationship between increasing patient survival times and aggressive surgical management in adults with supratentorial intermediate or high-grade astrocytomas, if patients receive postoperative radiotherapy.

KEY WORDS • astrocytoma • supratentorial tumor • prognosis • radiation therapy

The role of surgery to obtain a tissue diagnosis and to decompress mass effect in high-grade supratentorial gliomas in adults is a straightforward issue, whereas the oncological significance of aggressive tumor resection has been more difficult to assess. The first variable to be considered is the actual reduction in tumor burden accomplished by cytoreductive surgery, and the second variable is the effect of surgery on tumor cell behavior and kinetics. While these and related oncological issues remain to be further defined, the most basic measure of the success of cytoreductive surgery is long-term patient survival. In this review, we examine a number of major series published over the last 50 years to evaluate the effect of surgery on survival in adult patients with intermediate or high-grade supratentorial astrocytomas.

Prognostic Factors

Patient Age

There is substantial evidence suggesting an association between younger patient age and longer survival in adults with supratentorial intermediate or high-grade astrocytomas. Therefore, patient age should be carefully controlled in studies addressing the association between type of surgical management and duration of survival. A review of the literature, however, indicates wide variability in controlling for age.

Several studies have included patients less than 15 years old. In three studies, the youngest patient was 1 year old or less. The oldest patients in the studies defining this factor were 65 to 85 years old. In one very recent study, patients over 60 years old were reviewed. Several reports did not mention patient age, while others reported an important association between age and survival when age was analyzed as an independent variable but failed to take age into account when analyzing the association between type of surgical management and survival.

Avellanosa, et al., listed the ages of the patients studied but...
did not address the possible influence of age on the survival data reported. In the 1980 report of Scott and Gibberd, a younger age was associated with longer survival although age was not considered in the analysis of survival according to type of surgical therapy. Salamon et al. also did not account for patient age in his analysis, but earlier publications by the same author strongly suggested the dominant contribution of this factor in affecting patient survival. 139,145,146

Among studies that did account for age in the analysis of survival according to type of surgical management, several of these studies 33,38,62,66,89,96,108,155,158 examined the prognostic importance of age and all agreed on the importance of this variable in predicting survival time. There is, however, little agreement among these studies as to the effect of age on the relationship between the degree of surgical intervention and long-term survival. Some found a beneficial effect of aggressive tumor resection on survival 33,38,90,108,155,180 while others 38,62,66,148,177 could find no such relationship.

To summarize, there is strong evidence of an association between a younger patient age and longer survival times. Thus, age must be taken into account in measuring the effect of aggressive surgical intervention on patient survival, especially as several investigators have suggested that age may influence the selection of patients for specific surgical therapies. 1,38,47,74,141,161

Among studies that did account for age in the analysis of survival according to type of surgical management, there is little agreement concerning the survival benefit derived from aggressive surgical intervention.

Preoperative Functional Status

Several studies have reported a relationship between preoperative performance status and long-term survival. 2,33,38,66,74,96,108,132,139,173,174 Several investigations have also suggested that performance status may influence patient selection for different surgical therapies. 38,47,56,61,74,85,140,142 Indeed, Byar et al. stated that "... it is particularly important to consider this variable [performance status] when comparing nonrandomized series treated by different methods since differences in survival are likely to be much greater due to maldistribution of initial performance status than they are to differences in treatments received."

The omission of data pertaining to preoperative functional status is evident in a number of studies; several reports that argued for aggressive surgery made no consistent mention of patient preoperative clinical status. 3,47,56,116,123,140,142,152,162,165 Other studies reported an association between preoperative functional status and long-term outcome when the former was examined solely as an independent variable. 2,74,132 None of these studies, however, accounted for preoperative performance status in analyzing the relationship between the type of surgical management and long-term outcome.

Among studies that did account for patient function, there is little agreement concerning the association between long-term outcome and type of surgical management. 33,66,96,108,180 The Brain Tumor Study Group (BTSG) found that Karnofsky Performance Scale (KPS) rating and type of surgery were significantly related to period of survival when each of these factors was treated as an independent variable. Multivariate analysis, however, eliminated type of surgery as an important prognostic factor, whereas the KPS score was retained in the statistical model with lower preoperative KPS scores significantly associated with higher death rates. Kinsella et al. 96 reported that preadjuvant therapy performance status was the most significant prognostic variable while type of surgery had no impact on survival. By contrast, Chang et al. 33 and Nelson et al. 108 reported that both KPS rating and type of surgery were significantly associated with survival times. Wood et al. 110 included KPS rating in the regression analysis and reported that an increased postoperative area of contrast enhancement on computerized tomography (CT) was associated with a poorer survival prognosis. Even so, there was no statistically significant difference in survival times between patients having 75% or greater tumor resections and those having less than a 75% resection.

Investigators used various rating systems to document performance status, which may contribute to variability in reported results. 68,96 In addition, although the rating system developed by Karnofsky et al. 88 has been extensively used in the literature, patient stratification according to the KPS varied widely. The BTSG divided patients into four performance status groups (those with KPS scores of 10 to 40, 50 to 60, 70 to 80, and 90 to 100), whereas Nelson et al. 108 only included patients with a KPS rating of 40 or greater and divided patients into two groups (KPS scores of 40 to 70 and 80 to 100). Coffey et al. stratified patients into two groups (KPS scores of < 70 or 70 to 80), whereas Wood et al. 110 did not define how patients were grouped in relation to the KPS in their analysis. Some studies analyzed the importance of performance status prior to surgery, 2,33,38 and in others the patients' functional status was initially recorded after surgery but before adjuvant therapy. 56,96,108,155,180

Location of Tumor

The extent of surgical resection of supratentorial malignant neoplasms is often limited by the site and extent of the lesion. A desire to preserve neurological function dictates that tumors in ganglionic and eloquent brain areas be treated with biopsy or partial resection; lesions in noneloquent brain areas may be more aggressively resected. These considerations suggest that studies of the relationship between the degree of surgical intervention and survival need to account for tumor location.

Interpretation of data regarding tumor location is complicated by two factors. The first concerns the inaccuracy of pre-CT era estimations of tumor size and location. Nevertheless, CT scanning does not necessar-
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ily define the true extent of neoplastic involvement. Intermediate or high-grade astrocytomas may fail to enhance on CT scans and tumor cells may extend beyond the area of CT contrast enhancement or hypodensity, or beyond the area of increased signal intensity on T2-weighted magnetic resonance (MR) studies. However, CT and MR imaging are more specific and sensitive than earlier radiographic methods in defining areas of neoplastic involvement.

The second factor contributing to the variability in survival data is the multiplicity of ways in which tumor location may be defined or categorized for analysis. Location has been categorized according to: (1) hemisphere (dominant vs. nondominant); (2) specific lobe; (3) side and specific lobe; (4) number of lobes; (5) lobar versus nonlobar; (6) central versus noncentral; (7) deep versus superficial; or (8) supratentorial versus infratentorial. Even when similar grouping schemes are used, tumor sites within a single category may vary among studies. Also, several studies included, but did not necessarily account for, the presence of patient subsets with primary brain stem or cerebellar tumors.

Several studies either failed to consider tumor location in the data analysis or reported a relationship between tumor site and survival when the former was analyzed as an independent factor but did not consider tumor site as a covariant with other possible prognostic factors such as type of surgical therapy. Jelsma and Bucy made no mention of the possible relationship between tumor location and survival when tumor site was treated as an independent variable. Among the few studies that considered this factor in the analysis of the effect of surgery on survival time, only some may be interpreted to support aggressive tumor resection.

Tumor Pathology

In examining the association between the extent of surgical intervention and long-term survival, neither type of surgical therapy, the distribution of the different tumor types among patients with extensive resection, partial resection, and biopsy was not addressed. Furthermore, in a subsequent report that included patients reported in the 1967 study, Jelsma and Bucy made no mention of the possible relationship between tumor histopathology and period of survival.

In other reports, analysis of survival data according to type of surgery did not account for the presence of multiple, distinct neoplasms in the study population. Scott and Gibberd reviewed the survival characteristics of 95 patients with tumors classified according to the system of Russell and Rubinstein. Astrocytomas (grades I through IV), oligodendrogliomas, medulloblastomas, one ependymoma, and five tumors of "unknown" histology were represented among the 95 cases reviewed. Survival time after the first symptom appeared was correlated with the extent of surgery per-
formed, but no attempt was made to account for or document the distribution of the various histological types among the surgical groups.

The glioma classification system proposed by Kernohan, et al. 95 was used in seven studies. 2,4,89,148,162,165,177 Of these, several studies treated grades III and IV as a single pathological group. Whether this method affected the findings is open to question because several studies have shown differential survival in grade III and grade IV patients. 97,100,135,138,139,157,158,166 By contrast, others failed to substantiate the usefulness of dividing glioblastoma multiforme into these two grades. 33,48,110,145

The most basic question concerns the representation of different tumor grades in various surgical subgroups along with the influence of histopathology on outcome statistics. This is particularly important in light of recent evidence suggesting that a subgroup of patients with significantly longer survival emerges when tumors originally graded according to the Kernohan system as grade III or IV are reclassified according to the three-tier histological systems.33,110

Seven recent studies that investigated the importance of the degree of surgery used three-tier classification systems. 1,33,38,66,90,108,180 Of these studies, four reported an association between the extent of surgical intervention and period of survival, 1,33,108,180 whereas others found no such relationship. 38,96 The remaining study found extent of surgery to be significantly associated with period of survival when analyzed as an independent variable. When subjected to regression analysis, type of surgical therapy was eliminated as a significant variable from the model without a loss in the model’s ability to predict survival.

Therapeutic Considerations: Surgery

The first aim of surgery is to obtain an adequate tissue sample in order to arrive at a definitive diagnosis, and the second is to reduce intracranial pressure (ICP) when it is elevated. The surgical aim that is most controversial and difficult to assess is the usefulness of a “radical resection.”

Need for a Tissue Diagnosis

Because both prognosis and optimal therapy depend on a definitive diagnosis, the first purpose of surgery remains the establishment of a tissue diagnosis. The two surgical approaches to this problem are burr-hole biopsy and surgical resection via formal craniotomy.

In the early literature, several investigators noted the inaccuracy of available techniques for burr-hole biopsy and questioned its use, given the uncertainty about the area of tumor sampled. 47,162 Later investigators refined needle biopsy methods; recent data including two series of several hundred patients 3,18 indicate that accurate representation of the lesion is provided by tissue obtained with such methods. The technology has advanced such that multiple areas of the tumor with different radiographic appearance may be sampled. 33,44,90-92,106,118

Although needle biopsy techniques have increased in popularity, tumor resection via craniotomy remains the most commonly used method by which a diagnosis is established. 170,175 Several investigators have argued that one advantage of craniotomy and tumor resection over needle biopsy is the larger sample of tissue provided for pathological evaluation, 47,98,125,162 as the degree of anaplasia in astrocytomas is variable and the overall prognosis is determined by the most malignant portion of the tumor. However, recent refinements in biopsy techniques 3,32,39,90,99,118 may have minimized this advantage.

In the earlier literature, biopsy was associated with unacceptably high rates of morbidity and mortality frequently resulting in an increase in tumor edema in patients who already had marginal brain compliance. 56,74,84,85,162 Since that time, however, a number of technical advances have contributed to the present low morbidity and mortality rates associated with both needle biopsy and open resection techniques. 3,32,38,51,91,99,130

Needle biopsy and craniotomy techniques have similar morbidity and mortality statistics, and both techniques may be used to obtain a tissue diagnosis.

Reduction of Mass Effect

The second major aim of surgery in the management of supratentorial malignant astrocytomas is the relief of elevated ICP. Medical and radiographic advancements such as pharmacological agents to control intracerebral edema 57,58,82 and CT and MR imaging have had a major impact on patient management. After the introduction of steroids in the 1960’s, 57,58 elevated ICP could be lowered using medical means allowing time to prepare the patient for surgery and eliminating, to a large extent, the necessity for emergency craniotomy. 127-130,170 Given these nonoperative means of controlling ICP elevation, one may question whether tumor resection is necessary in the majority of cases to provide time for the completion of prescribed courses of adjuvant therapy. 139,141,154,175

Extent of Resection

The determination of the extent of surgical resection in supratentorial intermediate and high-grade astrocytomas is imprecise. Until the advent of CT, the degree of resection was defined by the surgeon’s impression of the amount of tumor removed at the time of operation. It has become apparent, however, that tumor is not limited to areas of contrast enhancement. 98,175 which defines the area of abnormal blood-brain barrier (BBB) and not the extent of tumor. 67,112,113 Similarly, tumor frequently extends beyond the area of hypodensity seen on CT scans 21,90,94,106 and beyond the region of abnormal signal on MR imaging. 99 Analogously, areas of tumor demonstrated by positron emission tomography scans or single photon emission CT scans do not necessarily coincide with those demonstr-
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Contrast-enhanced CT scans.106,107,120 Contrast-enhanced CT may delineate less than 50% of the actual tumor volume.90

Neuropathologists delineated malignant astrocytic cells distant from the solid tumor mass several years ago,149,150 and these findings have been substantiated by more recent clinical work.18,19,21,34,43-45,63,73,80,86,90-92.103,117,119,175 The failure in some studies to document distant tumor infiltration may be related to the fact that the nuclei of anaplastic cells may measure only 20 to 25 \( \mu \)m in cross-sectional area.18,64 and tumor detection may be influenced by tissue processing techniques.18,32,44,63,64 Intermediate and high-grade supratentorial astrocytomas in adults do not represent localized disease.8,11,69,75,140.

Some investigators have recently suggested that gadolinium-enhanced MR imaging may more clearly define the extent of tumor, but gadolinium-diethylene-triaminepenta-acetic acid (DTPA) does not cross an intact BBB and, thus, may not accurately identify tumor cells in brain regions distant from the site of increased BBB permeability.137 Whether gadolinium-enhanced MR imaging or in vivo MR spectroscopy will significantly improve the ability to identify the extent of tumor and the degree of tumor burden reduction accomplished by surgery remains to be determined. Recent studies have yet to demonstrate increased sensitivity or specificity of enhanced MR imaging, in comparison with available contrast-enhanced CT data, in defining the extent of tumor.15,30,52,94

Thus, even with currently available techniques, the approximate tumor burden reduction accomplished by aggressive surgery cannot be defined with accuracy. The 99% reduction approximated by postoperative enhancement is no more consistent than that of postoperative enhancement.141 The overwhelming majority of studies that addressed the role of surgery retrospectively reviewed the records of patients who were operated on by many different surgeons.4,33,47,50,56,62,66,74,76,90,108,111,115,119,123,140-142,148,162,165,171,177

One surgeon’s “total resection” may represent another’s “partial resection.” In addition, many studies did not define whether biopsy was performed via craniotomy or burr-hole biopsy.4,5,33,50,62,66,74,96,108,111,115,119,123,40-142,148,162,165,171 and an open biopsy to one surgeon may represent a “resection” or “partial resection” to a different surgeon. Only two studies documented the technical method by which needle biopsies were obtained. Among the few available CT-based studies,1,2,89,180 there is no consistency in the methods of estimating residual tumor volume or in the timing of the postoperative radiographic studies.

In many studies, patients who had tumor resection, regardless of the degree of resection, were considered as a single surgical group and their period of survival was compared with that of patients who underwent a biopsy only.4,9,33,47,62,74,89,96,108,111,115,123,140-142,148,165,177,180 Regardless of the groupings used, however, there is no general consensus concerning the effect of cytoreductive surgery on survival.

Lobectomy

When an attempt is made to clarify the influence on periods of survival of surgical procedures such as lobectomies, one encounters diverse and often uncontrolled methods among the various studies. Davis, et al.,47 and Frankel and German reported longer survival times in patients who underwent a lobectomy, although neither report accounted for the frequency of this procedure among the surgical groups investigated. Most studies did not mention lobectomy.4,2,3,33,38,50,96,108,111,115,116,123,132,148,162,165,171,180 when it was reported,62,74,121 the possible influence of this variable on the survival characteristics of the patients studied was not analyzed. In one study of the BTSG,171 approximately 20 patients had total resections, 109 had partial resections, and 78 had partial resections plus lobectomies. All of these patients were treated in the analysis as a single surgical group and were compared with 12 patients who were surgically managed with biopsy alone.

Multiple Operations

Another factor that may contribute to variability in reported results is the factor of reoperation. Careful

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control for this variable is indicated because patients undergoing multiple operations are not necessarily comparable with patients having a single operative procedure. A further review of the neurosurgical literature examining the role of surgery reveals that reoperation was either not mentioned or not consistently accounted for in the data analysis. Jelsma and Bucy computed the period of survival from the time of the second operation, but it is unclear how the remaining studies treated repeat operations in the data analysis. Also, lower-grade lesions were diagnosed at the time of the initial procedure in some of these reports. As documentation was not provided in several studies, these considerations give rise to the possibility that lower-grade lesions may have been included but not controlled for in the data analysis. Among more recent reports in which reoperation was not accounted for by study design, several investigators did not mention whether the patients underwent multiple surgical procedures.

Operative Mortality

A final surgical factor that may contribute to the lack of agreement in the data is surgical mortality. Until recently, tumor biopsy was associated with a substantially higher operative mortality rate in comparison with craniotomy and tumor resection. The manner of agreement in the data is surgical mortality. Until various collaborative studies regarding the association between periods of survival and type of surgery; in recent prospective collaborative efforts in which a significant difference in survival times was attributed to adjuvant therapy. In recent prospective collaborative efforts that carefully controlled for adjuvant therapy, the randomization process did not involve type of surgery. Rather, the importance of the degree of resection as a prognostic factor of survival was extrapolated by the use of regression model statistics. Such methods, however, do not substitute for studies specifically designed to test the efficacy of therapeutic interventions.

Radiation Therapy

External beam radiation has been consistently associated with prolonged survival in patients with supratentorial intermediate or high-grade astrocytomas. This association was suggested in several earlier retrospective studies. Several of the studies composing this review did not mention operative mortality but, given the disproportionate and no-longer-valid association between biopsy or limited tumor resection and increased operative mortality rate, one may question the influence of this factor on outcome data.

Adjuvant Therapy

A number of investigators have proposed that cytoreductive surgery is beneficial in reducing tumor burden and enhancing the probability of a favorable response to adjuvant therapy. To test this hypothesis, one must not only account for the extent of resection performed but also carefully define all adjuvant therapies administered.

A review of published reports discloses methodological problems in many studies with regard to adjuvant therapy, including: 1) no mention of adjuvant therapy; 2) treatment of both adjuvant therapy and type of surgery as independent variables; 3) multiple adjuvant therapies administered but not all therapies accounted for when computing the survival data according to type of surgery; and 4) the uncontrolled inclusion of subsets of patients drawn from parent prospective cooperative efforts in which a significant difference in survival times was attributed to adjuvant therapy. In recent prospective collaborative efforts that carefully controlled for adjuvant therapy, the randomization process did not involve type of surgery. Rather, the importance of the degree of resection as a prognostic factor of survival was extrapolated by the use of regression model statistics. Such methods, however, do not substitute for studies specifically designed to test the efficacy of therapeutic interventions.
ence in the long-term outcome of patients who received radiation therapy after tumor resections versus biopsies, although a statistical analysis was not performed. In another study, the survival characteristics of patients who had tumor resections were nearly identical to those of patients treated with only external decompression if postoperative irradiation was administered.\textsuperscript{44} Gehan and Walker,\textsuperscript{171} reported survival characteristics whereas Gehan and Walker examined the association between survival times and multiple variables of patients entered into study No. 69-01 of the BTSG. All patients received maximum surgical therapy followed by randomization to either conventional therapy (surgery and supportive care) or one of the adjuvant treatment arms of the study. Walker, et al.,\textsuperscript{172} reported that all adjuvant therapeutic regimens (radiation therapy, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), and radiation therapy plus BCNU) were superior to conventional care. Surgical biopsy was negatively correlated with period of survival. Using regression model statistics, Gehan and Walker reported that biopsy was negatively correlated with survival but only when adjuvant therapy was excluded from the statistical model. When adjuvant therapy was included in the model, type of surgery did not influence outcome, whereas radiation and chemotherapy were associated with longer survival.

In another cooperative study, the European Organization for Research on Treatment of Cancer (EORTC)\textsuperscript{50} reported that the length of postoperative survival was not related to type of neurosurgical procedure in patients receiving 5000 to 6000 rad. Scanlon and Taylor,\textsuperscript{148} in a series of patients who received split-dose radiation therapy, found no difference in actuarial survival when patients who had tumor resections or biopsies were compared. Similarly, Coffey, et al.,\textsuperscript{38} found that cytoreductive surgery was not a significant factor predictive of survival in patients who completed prescribed radiation. Newell, et al.,\textsuperscript{113} found that 3000 rad of whole-brain irradiation, administered over 10 days in a consecutive group of patients over 60 years old, resulted in a median survival time of 44 weeks following subtotal tumor resection compared with 15 weeks in the total resection group. Kinsella, et al.,\textsuperscript{96} reported that cytoreductive surgery had no significant effect on survival in a study in which 94% of the patients completed a planned course of hyperfractionated radiation therapy.

Overall, the findings of these studies argue against the efficacy of aggressive tumor resection in improving survival. However, the data from other investigations suggest otherwise. Jelsma and Bucy\textsuperscript{85} reported poor survival times in patients treated with external decompression or biopsy in comparison with others who had extensive tumor resection, although the proportion of patients in the biopsy group who received radiation therapy was not reported. Chang, et al.,\textsuperscript{33} found a relationship between type of surgery and period of survival in 554 patients entered into a Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group (RTOG/ECOG) protocol conducted between 1974 and 1979. Andreou, et al.,\textsuperscript{2} and Wood, et al.,\textsuperscript{180} retrospectively analyzed enhanced CT scans of subsets of patients entered into various protocols of the BTSG, and both investigators reported an association between postoperative area of enhancement and survival. Wood, et al., also reported, however, that when preoperative and postoperative studies were compared, the percentage of decrease in the area of enhancement (that is, estimated percentage of tumor resected) was not significantly correlated with survival. Nelson, et al.,\textsuperscript{106} reviewed the records of 94 patients with anaplastic astrocytomas who had been entered into various RTOG/ECOG protocols between 1973 and 1983. In this report, patients treated with tumor resection had longer median and 1- to 3-year actuarial survival in comparison with those treated with biopsy only. Similarly, Kelly\textsuperscript{48} reported poorer actuarial survival times in patients with grade IV thalamic glioblastomas treated surgically with biopsy only.

Interpretation of the available data is difficult because of the frequent omission of important parameters defining the radiation therapy administered. Nine studies did not report the dose of radiation administered.\textsuperscript{9,74,84,85,111,132,157,162,177} In three other studies\textsuperscript{47,56,165} widely varying dosages of radiation therapy were reported. In addition, none of these 12 studies documented the source, type, field, or fractionation schedule of the administered radiation. Each of these parameters, together with the total radiation dose, is an important variable that determines whether the administered treatment is ineffective, efficacious, or toxic.\textsuperscript{29,55,87,138,157,163,172,174,176} Other studies reported that irradiation, when analyzed as an independent variable, was associated with longer survival.\textsuperscript{28,47,56,74,84,85,111,132,152} In all of these studies only subsets of patients received radiation therapy, but this fact was not considered when survival data were analyzed according to type of surgical therapy.

In an attempt to control for the confounding influence of radiation therapy, Salcman\textsuperscript{140-142} selected 603 surgical cases from the earlier literature in which adjuvant therapy was not used. Although statistical comparisons were not performed, he concluded that the longest survival occurred in patients who underwent extensive resections, whereas the shortest survival was observed in patients treated with biopsy only. The relevance of these data to present-day management is questionable because no patient is optimally treated with only surgery, given the unsatisfactory results of this therapy alone.
Chemotherapy

Prospective randomized studies\textsuperscript{50,66} have reported significant effects of specific chemotherapeutic agents on the survival of glioma patients, although the efficacy of antineoplastic drugs in gliomas has been modest overall. Nevertheless, antineoplastic drugs may be associated with secondary toxicities that may adversely influence long-term outcome.\textsuperscript{4,33,96,169,172,179} Given these facts, it is important for any study addressing the efficacy of the extent of surgical resection to account for all chemotherapeutic agents administered to the study population.

Among recent studies, Scott and Gibberd\textsuperscript{152} reported that 41% of the 95 patients reviewed received "some form of chemotherapy." These patients had a survival time that was statistically significantly longer than those who did not receive chemotherapy. No information was provided concerning the general type of chemotherapeutic agents used, and the administration of chemotherapy was not accounted for when computing survival data according to the type of surgery. In the study of Andreou, et al.,\textsuperscript{2} all patients received 6000 rad of whole-brain radiation and most received carmustine, but the chemotherapy received by the remaining selected patients was not defined. Ammirati, et al.,\textsuperscript{7} and Newell, et al.,\textsuperscript{115} did not define types, dosages, methods of administration, or duration of chemotherapy received by subsets of patients included in their respective studies. Coffey, et al.,\textsuperscript{38} did not define the general parameters related to either the chemotherapy or the interstitial irradiation received by a representative portion of the study population; the possible influence of these treatment factors on the reported outcome data was also not considered.

In summary, multiple surgical and adjunctive therapeutic factors tend to confuse the data as to the effect of the extent of surgical intervention on long-term patient outcome. Coupled with this is the inherent inaccuracy of estimation of the degree of tumor burden reduction achieved by surgical resection. Intermediate and high-grade astrocytomas may not enhance,\textsuperscript{31,79} tumor cells have been demonstrated well beyond the areas of enhancement,\textsuperscript{19,21,25,43,45,79} and questions remain concerning the relationship between the timing of postoperative scans and surgically induced as opposed to tumor-induced enhancement.\textsuperscript{28,82,167} No CT-based studies included in this review\textsuperscript{1,2,89,180} controlled for administration of corticosteroids, even though these agents may clearly influence BBB permeability and CT enhancement.\textsuperscript{41,112,113} Other factors such as operative mortality, procedures such as lobectomies, repeat operations, and adjuvant therapies have not been taken into account by most studies. Among the few studies that did consider such factors, there is no agreement concerning the effect of aggressive tumor resection on long-term survival.

Study Design and Methods of Data Analysis

The association between type or extent of surgical intervention and survival times in patients with intermediate or high-grade supratentorial astrocytomas has not been studied prospectively according to a randomized design. Although the need for such a study may be debated,\textsuperscript{170} at present it is difficult, if not impossible, to assess precisely and scientifically the contribution of aggressive versus conservative surgical management to long-term survival. The present confusion and debate were recently documented in a survey of French neurosurgeons\textsuperscript{10} and were reflected at a recent meeting of the Congress of Neurological Surgeons.\textsuperscript{86,114}

Green and Byar\textsuperscript{65} proposed a hierarchy of strength of evidence model based on study design (Table 1). In almost all studies reviewed, the type and extent of surgical resection in most patients was not determined by the investigator. Patients were not randomly assigned to a given surgical therapy but were usually managed by multiple surgeons. Retrospective attempts to control for important patient characteristics such as age, KPS rating, and tumor location may begin to address the influence of possible prognostic factors, but questions persist concerning the comparability of the groups reviewed in regard to the type of surgery prescribed. In fact, most studies did not attempt to control for such factors. Recent work has definitively demonstrated the significance of prognostic variables on outcome.\textsuperscript{27,65,66,96,145,154,156,163,173,174,182}

Retrospective observational\textsuperscript{27} or survey\textsuperscript{161} studies help to define the natural course of a disease, identify possible prognostic factors, and may form the basis by which treatments may be tested in a randomized study. Such studies, however, fall short of definitively comparing treatments.\textsuperscript{27,105,161} It is noteworthy that the majority of the studies included in this review did not use any form of statistical analysis.\textsuperscript{27,4,9,47,56,74,84,85,116,123,132,140-142,152,156} They were included in this review because they form an important background upon which present attitudes are based, as exemplified by contemporary reviews.\textsuperscript{1,4,27,140-142,144,180} It is also striking that the methods used in several recent reports are similar to those used in studies conducted decades ago. This pertains not only

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1. Anecdotal case reports
2. Case series without controls
3. Series with literature controls
4. Analyses using computer databases
5. "Case control" observational studies
6. Series based on historical control groups
7. Single randomized controlled clinical trials
8. Confirmed randomized controlled clinical trials

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TABLE 1
Hierarchy of strength of evidence concerning efficacy of treatment

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to overall study design but also to the methods of data analysis. Even very recent reports used only first-order statistical analyses.\(^1\) Thus, the interaction and significance of multiple patient characteristics in regard to long-term survival and the possible influence of such factors on patient selection for a particular surgical intervention remain unclear in such reports.

Although recent cooperative groups have randomized patients according to adjuvant therapy, the randomization process did not involve type of surgical management. Furthermore, it was the explicit intent of the BTSG\(^{66,155}\) to perform maximum tumor resections, whereas the RTOG/ECOG\(^{33}\) made no such requirement. Thus, approximately 5% of the patients reported by the BTSG\(^{46}\) were treated surgically with biopsy only, whereas 25% of the patients studied by the RTOG/ECOG\(^{33}\) underwent biopsy only. The results of these cooperative groups differed with respect to the role of surgery, and the prognostic variables considered in the data analysis and the construction of the regression statistical model.\(^{40}\) In the report of Gehan and Walker,\(^{62}\) a step-up procedure was followed in constructing the statistical model; variables were added one at a time so that the statistical significance of adding patient characteristics at each stage could be calculated. The independent factor of adjuvant therapy was added after all other variables had been considered. By contrast, Green, \textit{et al.},\(^{66}\) used a step-down method in which factors were eliminated from the model if they did not have a significant effect on survival, given the other variables in the model. Adjuvant therapy was not considered or included at any time in the model. By further contrast, the first variable entered into the model by Chang, \textit{et al.},\(^{33}\) was adjuvant therapy, and this factor remained in the model regardless of the fact that no treatment option was found to be significantly better than a control. Other variables were then added until no additional variables were statistically significant. Wood, \textit{et al.},\(^{180}\) selected subsets of patients from a larger cooperative effort\(^{153-155}\) but did not describe the method of regression model construction. The influence of regression model construction on results derived from the statistical model has recently been reviewed.\(^{176}\)

The inclusion or exclusion of other factors and patient characteristics along with the definition of such variables also often differed among these studies. Pa
terial location was found by Gehan and Walker\(^{62}\) to be an important patient characteristic associated with poorer survival, whereas tumor location was not considered in the later studies conducted by the BTSG\(^{66,155}\) or in the analysis provided by Wood, \textit{et al.}\(^{180}\) Chang, \textit{et al.},\(^{33}\) and Green, \textit{et al.},\(^{66}\) included patient performance status, and both found that this factor remained an important prognostic factor in the regression analysis, whereas performance status was not considered by Gehan and Walker. In the study reported by Gehan and Walker, tumors were classified according to the systems of Kernohan, \textit{et al.}\(^{79}\) and Russell and Rubin-stein.\(^{134}\) Histopathology was not significantly related to survival time when analyzed as an independent variable and thus was not entered into the regression equation. By contrast, the classification system of Burger and Vogel\(^{22,23}\) was used in the subsequent studies of the BTSG,\(^{66,155}\) and histological category was found to be significantly related to period of survival not only as an independent variable but also as a prognostic covariate. Whether these differential results would have been substantiated if similar classification systems had been used in other reports of the BTSG is not clear.

Gehan and Walker\(^{62}\) reported that biopsy was a significant prognostic factor correlated with shorter survival when adjuvant therapy was not included in the regression model. The addition of adjuvant therapy to the statistical model eliminated type of surgical management from the model without a loss of the model’s ability to predict survival. Type of surgery was not a significant factor in the study of Green, \textit{et al.},\(^{66}\) even though adjuvant therapy was not included in the construction of that model. By further contrast, type of surgery was retained in the model constructed by Chang, \textit{et al.}\(^{33}\).

\textbf{Conclusions}

In the present communication, we have reviewed the three primary purposes of neurosurgical intervention in intermediate and high-grade supratentorial astrocytomas in adults. The need for tissue diagnosis and the importance of decompression in symptomatic patients is well established. Despite 50 years of study,\(^{61,136,151,163,168,175}\) however, the role of cytoreductive surgery, particularly as it relates to survival, remains unclear. Prognostic factors such as age, functional status, tumor histopathology, and tumor location are examples of variables that need to be taken into account. Since these variables interrelate, recent studies have used multivariate analysis. Unfortunately, no prospective studies have been done or are even planned to evaluate the role of aggressive surgery versus biopsy in the treatment of these tumors. Retrospective studies have demonstrated that aggressive surgical resection when it is the sole therapeutic modality may result in a modest increase in period of survival. On the other hand, in patients receiving postoperative adjuvant therapy, particularly irradiation, this increase in survival may not persist. Clearly, the only way to definitively answer these questions is with a randomized prospective study that is specifically designed to evaluate the role of surgery.

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