Low Grade Glioma: A Measuring Radiographic Response to Radiotherapy

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ABSTRACT: ***Purpose:*** We set out to determine the rate of response of low-grade (WHO Grade II) gliomas to radiotherapy and analyze the relationship between radiographic response, symptom control and patient survival. ***Methods:*** Patients were eligible for this study if they had received radiotherapy for pathologically confirmed, residual, supratentorial low-grade astrocytoma, oligodendroglioma, or mixed glioma, and imaging studies (baseline and follow-up) were available for review. Percent change in tumor size and rate and timing of response were determined by maximum linear measurement, area measurement, volume measurement using an ellipsoid model, and volume measurement by image segmentation. For each method, response to radiotherapy was defined firstly as a ≥ 50% decrease in tumor size (partial response), and secondly as a decrease equivalent to a 50% area decrease (normalized partial response). Relationships between radiographic response, clinical improvement and progression-free survival were analyzed using a Cox Proportional Hazard's model. ***Results:*** Twenty-one patients in a database (13 male, 8 female; ages 22-66 years) met the eligibility criteria. Twenty were imaged by computed tomography, 18 had an astrocytoma and 15 were irradiated soon after surgery. Responses were common and not felt to be due to a steroid effect. Use of normalized response criteria improved agreement between assessment of response as determined by the 4 methods. Median time to maximum radiographic improvement was 2.8 months (range, 1.5-11). Sixteen patients (76%) were improved neurologically, the median time to progression was 4.8 years and the 5-year progression-free survival rate was 43%. We did not detect a statistically significant association between response (as measured by any method), symptomatology and progression-free survival. ***Conclusions:*** Low-grade gliomas are moderately radioresponsive. Use of volume measurement may over-estimate the number of partial responses unless a volume reduction equivalent to a 50% area decrease is used to define response. The best way to measure response remains uncertain because neither visual, area, nor volume changes confidently predicted clinical outcomes.

RÉSUMÉ: Gliome de basse malignité: mesure radiologique de la réponse à la radiothérapie. ***But:*** Notre objectif était de déterminer le taux de réponse des gliomes de basse malignité (OMS grade II) à la radiothérapie et d'analyser la relation entre la réponse radiologique, le contrôle des symptômes et la survie. ***Méthodes:*** Les patients étaient éligibles à l'étude s'ils avaient reçu de la radiothérapie pour un astrocytome, un oligodendrogliome ou un gliome mixte supratentoriel résiduel de basse malignité confirmé par anatomopathologie et si des études d'imagerie (avant traitement et au cours du suivi) étaient disponibles. Le pourcentage de changement dans la taille de la tumeur, le taux et le moment de la réponse ont été déterminés par mesure linéaire maximum, mesure de la surface, mesure du volume au moyen d'un modèle ellipsoïde et mesure du volume par segmentation d'image. Pour chaque méthode, la réponse à la radiothérapie a été définie premièrement comme une diminution de ≥ 50% de la taille de la tumeur (réponse partielle), et deuxièmement comme une diminution équivalente à une diminution de 50% de la surface (réponse partielle normalisée). Les relations entre la réponse radiologique, l'amélioration clinique et la survie sans progression ont été analysées au moyen du modèle de régression des hasards proportionnels de Cox. ***Résultats:*** Vingt et un patients dont les observations étaient consignées dans la base de données (13 hommes et 8 femmes, âgés de 22 à 66 ans) remplissaient les critères d'inclusion. Chez vingt, une étude tomodensitométrique avait été faite. Dix-huit avaient un astrocytome et 15 ont reçu de la radiothérapie peu après la chirurgie. La réponse au traitement était fréquente et n'a pas été attribuée à un effet stéroïdien. L'utilisation d'un critère de réponse normalisé a amélioré la concordance entre les évaluations de la réponse par les 4 méthodes utilisées. La médiane du temps écoulé jusqu'à l'amélioration radiologique maximum était de 2.8 mois (de 1.5 à 11). Seize patients (76%) avaient une amélioration neurologique, la médiane du temps écoulé sans progression était de 4.8 ans et le taux de survie sans progression sur une période de 5 ans était de 43%. Nous n'avons pas détecté une association significative au point de vue statistique entre la réponse (quelle que soit la méthode de mesure), la symptomatologie et la survie sans progression. ***Conclusions:*** Les gliomes de basse malignité répondent modérément à la radiothérapie. L'utilisation de la mesure du volume peut surestimer le nombre de réponses partielles si une réduction du volume équivalente à une diminution de la surface de 50% est utilisée pour définir une réponse positive au traitement. Le meilleur moyen de mesurer la réponse demeure indéterminé parce que ni les changements de l'aspect, de la surface ou du volume n'ont pu prédire de façon fiable l'évolution clinique.

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For decades, the principal postsurgical treatment for low-grade (WHO Grade II) astrocytomas, oligodendrogliomas and mixed gliomas has been radiation,[1,2] and yet, there are few data in the literature describing the patterns of response of low-grade gliomas to radiotherapy, and no standard method for evaluating response. In this study, we examined the frequency, magnitude and time course of changes in tumor size after radiation in a cohort of

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patients with low-grade glioma and analyzed symptomatic improvement and progression-free survival as a function of radiographic response as estimated by four different techniques of measurement.

MATERIALS AND METHODS

Patient Selection and Treatment

Patients in this analysis were selected from a low-grade glioma database of 167 patients (1979-1995) compiled by Leighton and colleagues.[2] Eligibility criteria were set out in advance and included: pathologically verified supratentorial low-grade fibrillary astrocytoma, oligodendroglioma, or mixed glioma diagnosed between 01 January 1988 and 31 December 1995; age ≥ 18 years; treatment with radiotherapy; and a computed tomography (CT) or magnetic resonance (MR) scan prior to radiation demonstrating measurable tumor and at least one post-radiotherapy follow-up scan. Complete resection, unavailable or poor quality scans, radiotherapy elsewhere or prescribed for malignant transformation, or chemotherapy concurrent with radiotherapy rendered patients ineligible for this study. Age at diagnosis, gender, tumor location, tumor pathology and Karnofsky performance status (KPS) after surgery were retrieved from the database; extent of resection was estimated by comparing pre- and post-operative scans and designated a biopsy (≤ 25% removed) or partial resection (≥ 25% removed). All patients were treated with local field megavoltage (> 1.0 MV) radiation to doses from 5,000-6,000 cGy at 180-200 cGy/fraction over 5-6 weeks. Radiotherapy was delivered immediately after surgery or at the time of tumor progression following a period of observation. Patients were rescanned one month after completing radiotherapy and at 4-6 month intervals thereafter, or as dictated by clinical circumstances. Progression-free survival was defined as the interval from the start of radiotherapy to the date of tumor progression (as evidenced by clinical and radiographic tumor progression), or to the date of last follow-up.

Assessment of Tumor Size

For this analysis, the low density lesion on CT or the T2 abnormality on MR defined the tumor; foci of contrast enhancement within the lesion were evaluated separately. Tumor size pre- and post-radiotherapy was measured four ways: by using a segmentation model to approximate volume [(Σslice areas) x CT/MR slice thickness]; by using an ellipsoid model to approximate volume [π/6 x the product of the three largest perpendicular diameters], by calculating the product of the largest cross-sectional diameters on a transverse CT/MR image to approximate area and by measuring the largest linear dimension only. To measure response, the scan demonstrating the greatest size reduction after radiotherapy was used.

Response Evaluation and Statistical Considerations

Neurologic symptoms (seizures, headaches, focal deficits) post-radiotherapy were judged to be improved, unchanged, or worse by retrospective review of the patient's chart. Patients with decreased headaches or focal deficits or decreased frequency of seizures and who were on stable or decreasing doses of steroids post-radiotherapy were scored as "improved". Those with worse symptoms post-radiotherapy were scored as "worse". Those with stable or those with improved symptoms but increased steroids were scored "stable". Two definitions of partial response were considered. "Partial response" for any of the techniques of measurement was defined as a 50% reduction on the best post-radiotherapy scan versus the post surgical, pre-radiotherapy scan. Since a 50% volume reduction requires a smaller change in the overall dimensions as compared to a similar area reduction (and a 50% linear reduction corresponds to a larger area reduction) a "normalized partial response" was defined. The volume reduction and linear reductions corresponding to a 50% area reduction of a sphere are 65% and 30% respectively. Therefore, a "normalized partial response" for volume measurements was defined as a 65% or greater reduction and for linear measurements was defined as a 30% or greater reduction. By definition, the "normalized partial response" for area measurements remained at 50%. Partial responses and normalized partial responses between the four techniques of measurement was compared by Kappa Statistics. Absolute pre- and post-RT volumes and percent volume decreases as measured by the ellipsoid and segmentation methods were compared by student t-test and Pearson correlation coefficient. The relationship between radiographic response and clinical improvement was examined using the chi-squared test and the relationship between radiographic response and progression-free survival was analyzed using a Cox Proportional Hazards model. For each patient, steroid doses at the time of the baseline scan and follow-up scan used to assess response were recorded.

RESULTS

Patient Demographics

Twenty-one patients (13 male; 8 female) were eligible for this study; their median age at the start of radiotherapy was 39 years (range, 22-66). Twenty patients were imaged by CT, one by MR, and four had tumors that contained contrast-enhancing areas. The initial surgical procedure was a biopsy in 14 and subtotal resection in seven. Eighteen patients had an astrocytoma, one had an oligodendroglioma and two had a mixed glioma (i.e., oligoastrocytoma). Fifteen were irradiated immediately and six were treated at progression 8-141 months (median, 20) after diagnosis. The median treatment dose was 5,400 cGy (range, 5,040-6,000); the median number of fractions was 30 (range, 28-30); the median duration of follow-up was 52 months (range, 6-98); the median number of post-treatment scans available for review per patient was 8 (range, 2-13); and the median number of days from the start of radiotherapy to the post-treatment scan used to assess response was 87 (range, 49-340). Forty-one patients were excluded from this analysis for the following reasons: 11 had complete resections; 14 received radiotherapy elsewhere; two had palliative radiotherapy only; nine were treated for malignant transformation; two received chemotherapy concurrent with radiotherapy; and three had insufficient follow-up or poor quality scans.

Effects of Radiation on Symptoms and Tumor Size

Sixteen of 21 patients (76%) were improved neurologically following radiotherapy; seizures, in particular, often improved. Baseline and post-treatment tumor measurements are summarized in Table 1.There was a significant correlation between tumor size (both pre- and post-radiotherapy) as measured by the

Table 1: Changes in Tumor Size With Radiotherapy.

Tumor size	Pre	Post
Linear	7 cm (3-12)	5.6 cm (1.2-9.5)
Area	38.5 cm^2 (7.5-116)	28.8 cm^2 (1.44-69.5)
Volume (ellipsoid model)	80.5 cm^3 (9.8-487)	41.9 cm^3 (0.9-251)
Volume (segmentation model)	65.7 cm^3 (7.7-347)	27.7 cm^3 (1.19-196)

four methods. In particular, tumor size as assessed by maximum tumor diameters (linear, area, ellipsoid methods) were strongly correlated, as might be expected (correlation coefficients: 0.82 - 0.95; $p < 0.005$). Tumor size as assessed by image segmentation was less strongly correlated with the other methods (correlation coefficients: 0.51 - 0.94; $p < 0.05$) reflecting the inaccuracy of spherical/ellipsoid models in approximating a complex tumor shape like an infiltrating glioma. In particular, tumor volume estimates before and after radiation were larger using the ellipsoid approximation than the segmentation method, especially for larger tumors with complex shapes. Correlation between the two volume methods were 0.622 ($p = 0.003$) and 0.943 ($p = 0.000$) for the pre- and post-treatment volumes respectively.

There was a statistically significant correlation between linear, area and volume assessments of percent change in tumor size (correlation coefficients: 0.78 - 0.92, $p < 0.003$). Rates of response, (partial and normalized partial response) are summarized in Table 2. As anticipated use of a 50% cutoff resulted in a larger number of partial responders as assessed by the volumetric (ellipsoidal and segmented) methods of measurement and a fewer number of responders when a single linear measurement was used. Use of the normalized 50% response criteria generally improved the agreement between response as assessed by the four methods of measurement (Table 3). Disagreement between the ellipsoid and segmentation methods of assessing volume response existed even with the normalized partial response criteria. Most of the disagreement occurred at response levels close to the normalized partial response cutoff where small differences in volume as assessed by the two methods led to disagreement in detecting responders (Figure). Since gliomas are not uniformly shaped tumors, this disagreement was not unexpected. If response is to be determined on the basis of volume changes, the segmentation techniques may be preferable over the simpler (but less precise) ellipsoid approximation of tumor volume as the ellipsoid method tended to "overcall" responders.

Table 2: Response to Radiotherapy.

Method of Measurement	Median % (Range) Decrease	Partial Response	"Normalized Partial Response"*
Linear	23% (-11-60)	3/21	6/21
Area	50% (-34-83)	11/21	11/21
Volume Ellipse	65% (-61-90)	14/21	12/21
Volume Segmented	59% (-11-91)	14/21	8/21

* See Text

Table 3: Agreement Between Partial Response Versus Normalized Partial Responses.

Partial Response

	Linear	Area	Ellipsoid	Segmentation
Linear		81%	67%	67%
Area	81%		86%	67%
Ellipsoid	81%	81%		81%
Segmentation	86%	76%	76%	

Upper right figures demonstrate agreement (Kappa Statistic) between methods of response determination when a uniform 50% response criterion is applied. Lower left figures demonstrate agreement when the response criteria is normalized to a 50% area reduction. (All figures statistically significant at $p < 0.05$ except *P = 0.06.)

The median time to maximum response was 2.8 months (range, 1.5-11). CT images worsened transiently in two patients, one before and one after maximum response; both had low grade tumors when re-biopsied, improved spontaneously and did well subsequently. Foci of contrast enhancement decreased in size in the three patients in whom this radiographic feature could be assessed longitudinally. For patients in this study, the median time to tumor progression calculated from the start of radiotherapy was 4.8 years (5.2 years from diagnosis) and the 5-year progression-free survival rate was 43%. These results were comparable (not statistically different) from the larger database of patients with low grade glioma from which our subset was taken. Nineteen patients were off steroids or on a lower dose at the time of the scan used to assess response; one responder (50% change) and one non-responder (< 25% change) were on a higher dose.

Clinical Endpoints vs. Radiographic Response

By all methods of evaluation, more partial responders improved symptomatically than non-responders, but in no instance did the association between radiographic response (by any method) and clinical improvement reach statistical significance. Small sample size and the retrospective assessment of clinical improvement may have contributed to this lack of statistical significance. Likewise, there was no statistically significant link between radiographic response and baseline tumor size, percent size decrease, response rate, or progression-free survival.

DISCUSSION

This study suggests that low-grade gliomas are moderately radioresponsive neoplasms. Partial responses were common and not a steroid effect. Neurologic symptoms and computed tomography images improved within three months in most instances. Our finding that low-grade gliomas often respond to radiotherapy is consistent with earlier work. Eyre et al.[3] reported that 80% (15/19) of patients in the control arm of a randomized trial evaluating chemotherapy for incompletely resected low-grade glioma responded to radiation. Response in this CT-based study was defined as neurologic improvement accompanied by a 50% or greater decrease in the tumors' maximum cross-sectional area. Using similar criteria, Lunsford et al.[4] reported that 46% (17/35) of patients with low-grade responded to radiotherapy; in our study, clinical improvement and a 50% or greater decrease in maximum cross-sectional area were observed in 52% (11/21). We do not know whether our findings with respect to changes in

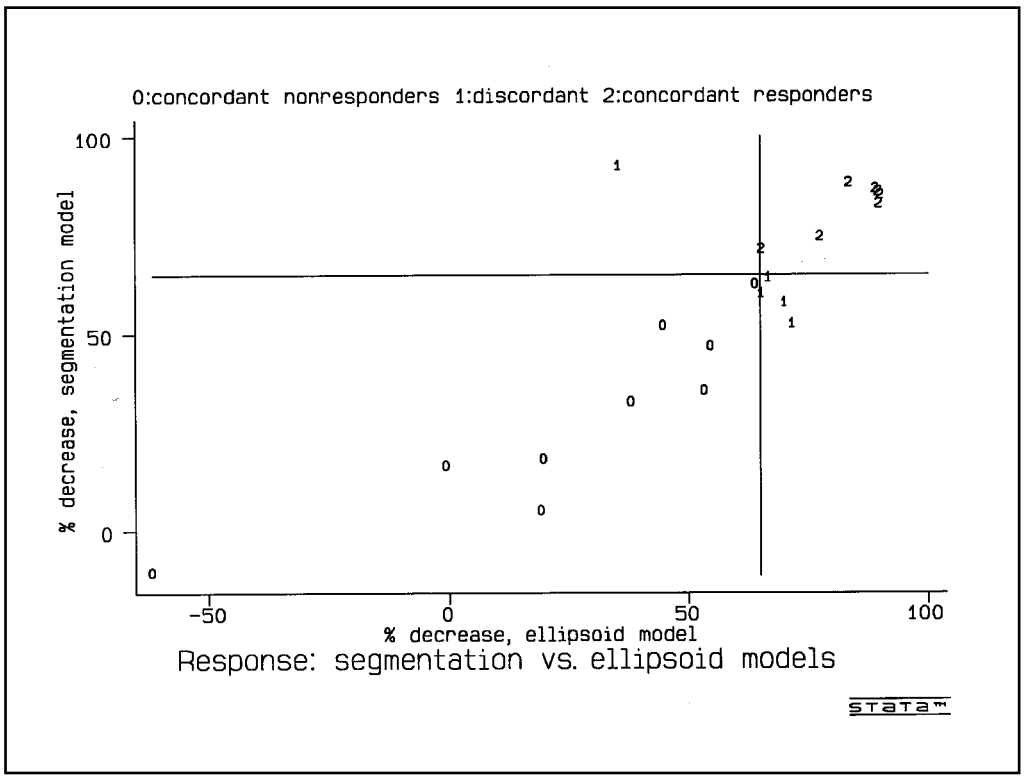

Figure: *Normalized partial responders as determined by ellipsoid and segmentation methods of volume response. Vertical and horizontal lines delineate 65% volume decrease. 0, 2 indicate agreement between the two methods, 1 indicates patients classified as normalized partial responders by one but not both methods.*

tumor size and rates of response to radiotherapy can be generalized to all patients with low-grade glioma, as this study was conducted retrospectively. However, the median progression-free survival time for patients in this analysis was similar to that of all patients with low-grade glioma seen at our centre since 1979 (5.2 vs. 4.9 years), an observation suggesting that the patients in this study were a representative subset of the larger group.

Although statistically speaking, visual, area and volume determinations of percent change in tumor size and rates of partial response were similar, numerical values differed considerably. In general, methods that relied on measurement of 1-3 tumor diameters were well correlated among each other but less so with a precise volume determination as accomplished by image segmentation. A 3-dimension measurement (ellipsoid method) correlated the best with the image segmentation but still tended to overestimate tumor size.

As pointed out by Chapell et al.,[5] application of a 50% response criterion to volume changes can inflate response rates as compared to area measurements purely on mathematical grounds (volumeαarea$^{3/2}$). We confirmed that volume models rendered liberal interpretations of percent change in tumor size and response when conventional 50% response criteria were applied. Use of response criteria normalized to a 50% decrease in area (normalized partial response) improved agreement between response as measured by changes in maximum linear size, area or volume of the tumor. In general the ellipsoid and image segmentation assessments of normalized partial response agreed except for borderline responders where subtle differences in volumes arose between the two methods. The ellipsoid model has the advantage of ease of use over image segmentation which can be quite time consuming to accomplish, however the ellipsoid measurement may be inaccurate particularly in these "borderline" responders. However, until it can be demonstrated that the precision of volume measurements with image segmentation predicts clinical improvement or progression-free survival more accurately than the ellipsoid, or area approximations, all methods of assessing response may be of equal value. While the optimal method for measuring the effects of radiation or other therapies on glial tumors remains uncertain it is evident from this analysis that response rates as reported in Phase II clinical trials[6] may be influenced by tumor measurement techniques. As a consequence, the method of determining response must be stated explicitly in the methods section of brain tumor studies to facilitate response rate comparisons between older series (where visual or area measurements were used) and newer ones (where volumetric measurements are more common). In particular, if tumor volume measurements are used, response rates should be normalized to those conventionally used for changes in tumor area (i.e., a 65% volume reduction) and the method used to determine volume stated. Ideally, area-based response rates should also be reported in conjunction with volume-based response rates to facilitate comparisons between series. Use of such "normalized partial response" criteria would help avoid the possibility of overcalling (or undercalling) responders and in doing so mistake a measurement artifact for a therapeutic effect.

We observed no correlation between size reduction and patient outcome, a recurring theme in neuro-oncology. Many investigators now question whether tumor shrinkage is an

important measure of treatment effect for glial tumors.[7] In this regard, three recent studies are of interest. For oligodendrogliomas treated with PCV, Cairncross and colleagues[8] observed long progression-free intervals for complete and major partial responders (≥ 90% area decrease) whereas times-to-progression were similar for patients with partial responses (50%) and stable disease. Cairncross and Eisenhauer[9] speculated that neuro-oncologists would not detect a relationship between radiographic response and tumor control until highly effective therapies generating substantial numbers of complete responses emerged. Experience with chemotherapy for embryonal tumors of the CNS supports this hypothesis. Galanis et al.[10] observed that platinum-based regimens induced complete remissions with long periods of tumor control, whereas nitrosourea-based therapies rarely induced complete responses and progression-free intervals were indistinguishable for patients with partial response (≥ 50% area decrease) or stable disease. Similarly, using CT scanning and visual evaluation of high grade glioma, Barker et al.[11] observed that unequivocal responders to radiotherapy lived significantly longer than patients with unequivocal tumor progression, while noting similar durations of survival for those with minor scan improvement, minor scan worsening, or stable disease. Future studies with larger numbers of patients with low-grade glioma to enhance statistical power, or conducted prospectively and using MR imaging, may yet demonstrate a direct relationship between radiographic response and clinical endpoints; however we were unable to detect such an effect.

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