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Magnetic resonance imaging volumetric assessment of the extent of contrast enhancement and resection in oligodendroglial tumors

Clinical article

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Object. Oligodendrogliomas that enhance on MR images are associated with poor prognosis. However, the importance of the volume of enhancing tumor tissue, and the extent of its resection, is uncertain. The authors examined the prognostic significance of preoperative and residual postoperative enhancing tissue volumes in a large single-center series of patients with oligodendroglioma. They also examined the relationship between enhancement and characteristic genetic signatures in oligodendroglial tumors, specifically deletion of 1p and 19q (del 1p/19q).

Methods. The authors retrospectively analyzed 100 consecutive cases of oligodendroglioma involving patients who had undergone T1-weighted gadolinium-enhanced MRI at diagnosis and immediately after initial surgical intervention. The presence of preoperative enhancement was determined by consensus. Preoperative and residual postoperative volumes were measured using a quantitative, semiautomated method by a single blinded observer. Intrarater reliability for preoperative volumes was confirmed by remeasurement in a subset of patients 3 months later. Intrarater and interrater reliability for residual postoperative volumes was confirmed by remeasurement of these volumes by both the original and a second blinded observer. Multivariate analysis was used to assess the influence of contrast enhancement at diagnosis and the volume of pre- and postoperative contrast-enhancing tumor tissue on time to relapse (TTR) and overall survival (OS), while controlling for confounding clinical, pathological, and genetic factors.

Results. Sixty-three of 100 patients had enhancing tumors at initial presentation. Presence of contrast enhancement at diagnosis was related to reduced TTR and OS on univariate analysis but was not significantly related on multivariate analysis. In enhancing tumors, however, greater initial volume of enhancing tissue correlated with shortened TTR ($p = 0.00070$). Reduced postoperative residual enhancing volume and a relatively greater resection of enhancing tissue correlated with longer OS ($p = 0.0012$ and 0.0041, respectively). Interestingly, patients in whom 100% of enhancing tumor was resected had significantly longer TTR (174 vs 64 weeks) and OS (392 vs 135 weeks) than those with any residual enhancing tumor postoperatively. This prognostic benefit was not consistently maintained with greater than 90% or even greater than 95% resection of enhancing tissue. There was no relationship between presence or volume of enhancement and del 1p/19q.

Conclusions. In enhancing oligodendrogliomas, completely resecting enhancing tissue independently improves outcome, irrespective of histological grade or genetic status. This finding supports aggressive resection and may impact treatment planning for patients with these tumors.
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Key Words • **oligodendroglioma** • **prognosis** • **contrast enhancement** • **resection** • **volumetric analysis** • **oncology** • **survival**

Oligodendroglial tumors are predominantly supratentorial, diffuse primary brain tumors and represent the second most common glioma in adults after glioblastoma multiforme.[11] Closely related to diffuse fibrillary astrocytomas both clinically and biologically, they are classified as pure oligodendrogliomas or mixed oligoastrocytomas and are graded histologically as low grade (WHO Grade II) or anaplastic (WHO Grade III).[20] Similar to fibrillary astrocytomas, oligodendroglial tumors that show enhancement on conventional MRI after administration of gadolinium contrast medium have long been thought to portend a poorer prognosis.[18,22] In fact, the presence of contrast enhancement has been considered a central criterion in some grading systems for oligodendroglial tumors.[10] Furthermore, the presence of

Abbreviations used in this paper: DICOM = Digital Imaging and Communications in Medicine; ICC = intraclass correlation; MIPAV = Medical Image Processing and Visualization; OS = overall survival; TTR = time to relapse; VOI = volume of interest.

new foci of enhancement in a previously nonenhancing tumor is usually considered highly suggestive of malignant degeneration.[7,8] Recent work, however, suggests a weaker correlation between tumor enhancement and histological grade than originally thought: Many anaplastic oligodendroglial tumors do not enhance, while a significant minority of low-grade ones do.[12,37]

Current treatment strategies for oligodendroglial tumors include—either individually or in combination—observation with serial imaging, biopsy alone, resective surgery, radiotherapy, and chemotherapy. However, the optimal management of these tumors, especially those graded as WHO Grade II, remains uncertain.[21] In particular, the timing and extent of resection and its impact on survival are controversial. In most centers, resective surgery is offered for biopsy-proven or suspected oligodendroglial tumors that are 1) causing symptomatic mass effect, 2) causing epilepsy, or 3) demonstrating unequivocal growth on serial imaging studies. Surgery is also commonly offered when tumors demonstrate contrast enhancement at diagnosis or enhance on follow-up imaging. It has not yet been shown conclusively that more extensive resection improves survival in patients with these tumors. Furthermore, no published studies have used quantitative volumetric methods to assess extent of resection, nor has the prognostic significance of residual contrast-enhancing tumor after surgery been examined specifically. Addressing the question of resection is particularly relevant given that oligodendroglial tumors exhibiting deletion of chromosome regions 1p and 19q (del 1p/19q) are highly sensitive to chemotherapy.[4,5] These tumors also have a more favorable natural history,[14,33] which suggests that a less aggressive approach to surgery altogether may be a reasonable approach in patients in this subgroup. Unfortunately, the relationship between contrast enhancement and del 1p/19q—among other molecular signatures—is also unclear.

We therefore were interested in the significance of contrast enhancement as it relates to the prognosis and surgical management of oligodendroglial tumors. Specifically, our objectives were: 1) to determine the independent prognostic significance of contrast enhancement on MRI at diagnosis in adults with a supratentorial oligodendroglial tumor; 2) to determine the prognostic significance of the initial volume of contrast-enhancing tissue and the presence and volume of residual enhancing tissue after resection in patients with enhancing tumors; and 3) to determine if preoperative contrast enhancement and common genetic alterations in oligodendroglial tumors, most notably del 1p/19q, were correlated.

Methods

Patient Selection

The comprehensive, prospectively updated brain tumor database at the Barrow Neurological Institute of St. Joseph's Hospital and Medical Center was queried to identify all patients with a histological diagnosis of an oligodendroglial tumor whose initial surgical procedure (biopsy or resection) was between January 1992 and January 2001. Two hundred thirteen patients met these criteria. Of these, patients included in the study had to meet 3 additional criteria: 1) they had undergone preoperative axial T1-weighted MRI with gadolinium contrast medium; 2) they had also undergone an immediate postoperative (within 72 hours) axial T1-weighted MRI with gadolinium contrast medium; and 3) their archived pre- and postoperative MRI studies were available in DICOM format for image processing. Altogether, 100 patients (55 male, 45 female) met these criteria for inclusion.

Patient Treatment

All cases involving patients in the study were reviewed by an institutional tumor board. Treatment plans for each patient were reached by consensus between neurosurgery, radiation oncology, and neurooncology specialists. In particular, the decision to treat up front with radiation or chemotherapy was made on a case-by-case basis.

Image Processing and MRI Volumetric Analysis

Digital MR images in DICOM format for each patient were stripped of overt identifiers, numerically coded, and stored on a personal computer workstation. Image processing was completed with the freely available, public domain MIPAV version 4.0 software package (Medical Image Processing and Visualization, National Institutes of Health). The MR images were first transformed into normalized Talairach image space to account for variations in image acquisition and head shape.[35] They also underwent standard automated correction for intensity nonuniformity due to radiofrequency inhomogeneity of the MRI scanner and intensity standardization using the inhomogeneity N3 algorithm included in MIPAV, based on the method published by Sled et al.[32] Two trained observers (authors T.S. and N.Z.M.) determined the presence or absence of contrast enhancement on each scan by consensus. Volumetric segmentation of enhancing tumor tissue was then completed by a single trained observer blinded to patient identity (N.Z.M.). We assessed intrarater reliability for preoperative enhancing tumor volume by having the same observer (N.Z.M.) resegment the scans in 20 randomly selected cases 3 months later. For postoperative residual enhancing volume, we assessed intrarater reliability by having the original observer (N.Z.M.) resegment enhancing tissue on all postoperative scans 1 year after initial segmentation. Given the importance of the volume of residual postoperative enhancing tumor tissue in this study, we further assessed interrater reliability by having a second blinded observer (J.J.) also segment residual enhancing tissue on all postoperative scans.

We used a semiautomated method to segment enhancing tumor tissue in each patient. The process involved first selecting a seed voxel in an area of obviously enhancing tumor tissue on an axial T1-weighted MRI slice. Next, we applied the "Paint Grow" algorithm within MIPAV to include all adjacent enhancing voxels on the same slice whose intensity was between 20% below and 20% above the intensity of the enhancing index voxel (Fig. 1). The process was repeated for every tumor-containing slice in the MRI study for each patient. The trained observer then

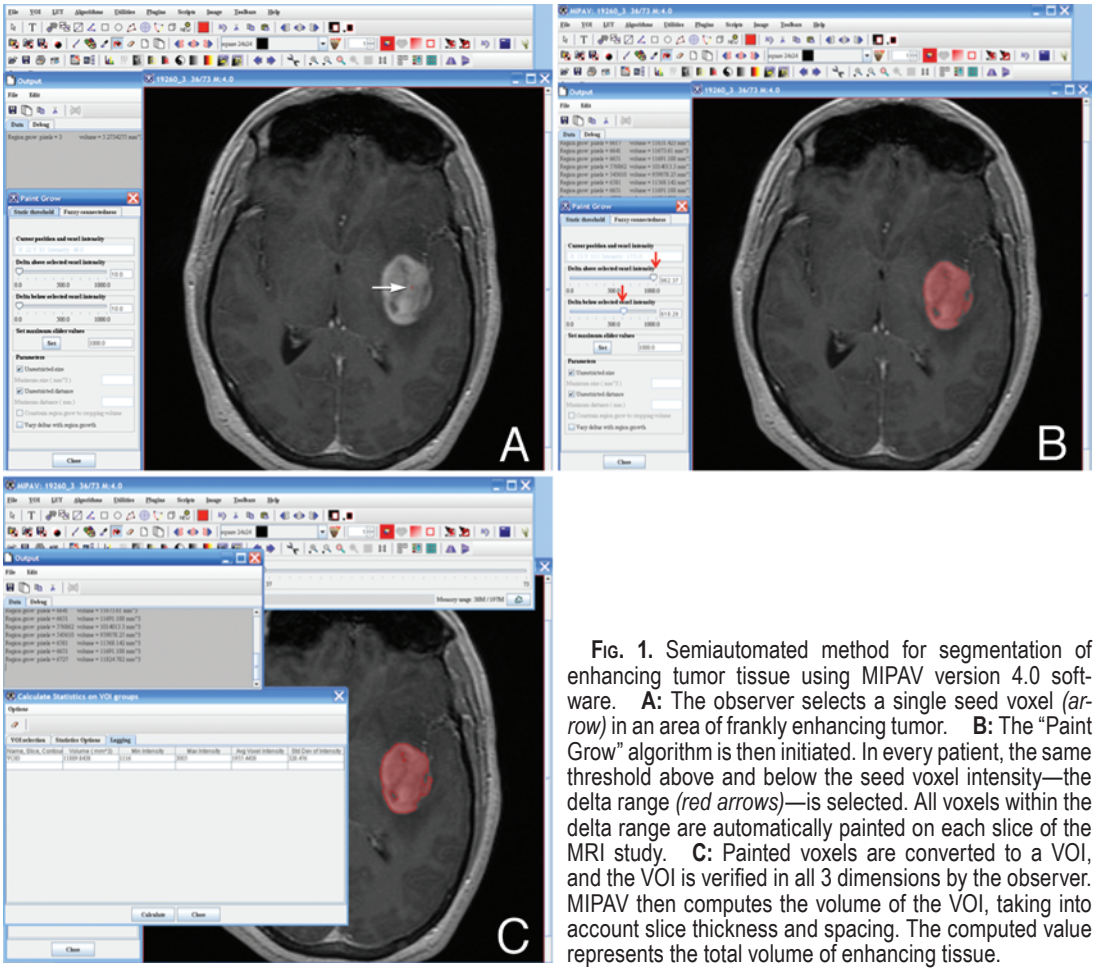

Fig. 1. Semiautomated method for segmentation of enhancing tumor tissue using MIPAV version 4.0 software. **A:** The observer selects a single seed voxel *(arrow)* in an area of frankly enhancing tumor. **B:** The "Paint Grow" algorithm is then initiated. In every patient, the same threshold above and below the seed voxel intensity—the delta range *(red arrows)*—is selected. All voxels within the delta range are automatically painted on each slice of the MRI study. **C:** Painted voxels are converted to a VOI, and the VOI is verified in all 3 dimensions by the observer. MIPAV then computes the volume of the VOI, taking into account slice thickness and spacing. The computed value represents the total volume of enhancing tissue.

performed manual correction in the axial, coronal, and sagittal planes. Areas of obvious cyst or necrosis were excluded. Special care was taken on postoperative scans to avoid including adjacent vessels that might otherwise be considered erroneously to represent residual enhancing tumor tissue. Painted areas in each slice were summed to create a VOI. The volume of the VOI (representing the total volume of contrast-enhancing tissue in a given patient) was then computed by MIPAV, taking into account slice thickness and interslice spacing.

Deletion Analysis of 1p/19q

Deletion analysis was done using fluorescence in situ hybridization. Unstained sections of 5-μm thickness were deparaffinized in xylene, placed in Lugol iodine solution for 5 minutes, washed in 2.5% sodium thiocyanate until clear, and then dehydrated in ethanol. The slides were placed in 10 mM citric acid (pH 6) and microwaved on high for 5 minutes. The sections were then digested in a pepsin/0.9% NaCl solution, pH 1.5, for 60 minutes at 37°C, dehydrated in graded ethanols, and air dried. Del 1p/19q was determined using the Vysis LSI 1p36/LSI 1q25 and LSI 19q13/19p13 dual-color probes (Abbott Molecular). Probes for del 1p/19q were placed on the slides, sealed under a coverslip, denatured at 80°C for 3 minutes, and hybridized for 24 hours at 37°C. Slides were then washed in 1.5 M urea/0.1× saline–sodium citrate for 15 minutes at 45°C, rinsed briefly twice with saline–sodium citrate and then dried in darkness. Counterstaining was done using Vectashield counterstain with 4′,6-diamidino-2-phenylindole (DAPI, Vector Laboratories).

Fluorescence in situ hybridization results were viewed on a Zeiss Pascal 5 laser scanning confocal microscope (Carl Zeiss, Inc.). For each hybridization, signals were counted in at least 80 cells in the region of the tumor specified by the neuropathologist. Deletion of chromosome region 1p was determined using a probe for 1p36 with a control probe for 1q36. Deletion of chromosome region 19q was determined using a probe for 19q13 with a control probe for 19p13. Deletion was defined as probe signal loss in the presence of a control signal for each chromosome copy. A normal ratio was approximately 1.0. Any ratio less than 0.8 and/or the presence of more than 20% individual nuclei with deletion was scored as deleted.

Study End Points and Statistical Analysis

Clinical follow-up for all 100 patients was available through 2007. Primary outcome measures were 1) time to relapse (TTR) and 2) overall survival (OS). Relapse was defined by the occurrence of one of the following: reoperation, tumor progression on imaging, or a change

in therapy. Patients who had not relapsed or who were still alive at the end of the follow-up period were right-censored in any statistical analyses.

The entire patient cohort (n = 100) was used to assess the impact of contrast enhancement at diagnosis on TTR and OS. Only cases in which patients had preoperative contrast enhancement (n = 63) were used to assess the impact of pre- and postoperative enhancing tumor volume on outcome. Volumetric data were analyzed both using continuous variables (preoperative volume, postoperative volume, % resection of enhancing tissue) and using nominal variables (100% resection, > 95% resection, and > 90% resection of enhancing tissue).

Univariate analysis was achieved by comparing Kaplan-Meier survival curves for patients in distinct groups (for example, enhancing vs nonenhancing) using the log-rank test. A threshold of $p < 0.05$ was used for statistical significance. Survival curves were plotted and analyzed using GraphPad Prism software version 4 (GraphPad Software, Inc.). Multivariate analysis was performed using Cox proportional hazards regression modeling controlled for confounding clinical, pathological, and molecular variables, including sex, age, presence of an astrocytic component, WHO grade, presence of a cystic component, MIB-1, Ki 67 labeling index, early and late radiotherapy, early and late chemotherapy, del 1p/19q, 1p ratio, 19q ratio, % 1p loss, % 19q loss, 1p deletion, 19q deletion, epidermal growth factor receptor amplification, and chromosome 7 polyploidy. The threshold of statistical significance was set at $p < 0.05$. Three different multivariate analyses were performed: 1) for the entire patient cohort (Table 1), with enhancement as a categorical variable (present vs absent); 2) for the enhancing subgroup, with volume of enhancement as a continuous variable; and 3) for the enhancing subgroup (Table 2), with volume of enhancement as a nominal variable. All multivariate analyses were performed using SAS/STAT software version 8.2 (SAS Institute, Inc.).

Both intra- and interrater reliability were expressed as percentages computed by the following formula: % difference = (100 × |a—b|/a), where a represents the first measured volume and b represents the volume measured at a later time either by the same observer or by a different observer. Both intra- and interrater agreement were also assessed by computing an intraclass correlation (ICC) statistic. An ICC coefficient greater than 0.8 signifies excellent concordance between 2 raters.[31] The ICC coefficients were calculated using IBM SPSS Statistics software for Mac version 19, release 19.0.0 (IBM, Inc.).

TABLE 1: Clinical, pathological, and biological characteristics across all patients*

Clinical Variable	Value
total no. of pts	100
mean age (yrs)	42.6 ± 12.7
sex (no. of male pts)	55
median time to relapse (wks)	113
median survival (wks)	257
cystic tumor	29
astrocytic component	51
malignant (WHO Grade III)	38
MIB-1 >10%	43
mean Ki 67 labeling index	6.68 ± 8.35
early radiotherapy (at time of first diagnosis)	48
late radiotherapy (at time of relapse)	36
early chemotherapy	33
late chemotherapy	48
LOH 1p/19q	13
1p deletion	28
19q deletion	20
mean 1p ratio	0.88 ± 0.17
mean 19q ratio	0.92 ± 0.14
mean % 1p loss	23.12 ± 31.46
mean % 19q loss	16.70 ± 27.76
EGFR amplification	7
chromosome 7 polyploidy	25

* EGFR = epidermal growth factor receptor; LOH = loss of heterozygosity; pts = patients.

Results

Presence and Distribution of Preoperative Contrast Enhancement

On initial imaging 63% of tumors showed contrast enhancement. Of WHO Grade II tumors, 41.94% enhanced (Table 3), whereas 97.37% of WHO Grade III tumors enhanced (that is, all but 1 WHO Grade III tumor). This difference was statistically significant ($p = 0.02$).

Volumetric Data

On average, 86.26% of enhancing tumor tissue was resected (Table 3). In only 16 (25.40%) of 63 patients was complete resection of all enhancing tissue achieved.

Intrarater and Interrater Reliability

For preoperative enhancing tumor volume, intrarater reliability calculated from a resegmentation by original observer N.Z.M. of 20 randomly selected patient scans was 11.89%, which corresponded to a robust ICC coefficient of 0.85 (95% CI 0.77–0.93, $p < 0.01$), indicating excellent concordance (Fig. 2).

For postoperative residual enhancing tumor volume, intrarater reliability calculated after resegmentation of all patient scans by original observer N.Z.M. was 5.92%, with a corresponding ICC coefficient of 0.83 (95% CI 0.72–0.90, $p < 0.0001$) signifying excellent concordance. Interrater reliability (that is, original volumes segmented by observer N.Z.M. compared with volumes segmented by observer J.J.) was 7.29%, with a corresponding ICC coefficient of 0.95 (95% CI 0.91–0.97, $p < 0.0001$) signifying even stronger concordance. Phrased differently, mean residual enhancing tumor volume based on the original observations of observer N.Z.M. (Table 3) was 2.36 ± 3.85 cm^3 (mean percentage resection of 86.26% ± 19.49%). Repeat segmentation by observer N.Z.M. revealed a mean residual enhancing tumor volume of 2.47

TABLE 2: Clinical, pathological, and biological characteristics across patients with enhancing tumors only

Clinical Variable	Value
total no. of pts	63
mean age (yrs)	43.6 ± 12.9
sex (no. of male pts)	37
median TTR (wks)	83
median OS (wks)	196
cystic tumor	26
astrocytic component	34
malignant (WHO Grade III)	37
MIB-1 >10%	34
mean Ki 67 labeling index	8.76 ± 9.53
early radiotherapy	38
late radiotherapy	15
early chemotherapy	26
late chemotherapy	29
LOH 1p/19q	10
1p deletion	17
19q deletion	15
mean 1p ratio	0.88 ± 0.16
mean 19q ratio	0.91 ± 0.15
mean % 1p loss	21.27 ± 30.75
mean % 19q loss	17.92 ± 28.52
EGFR amplification	6
chromosome 7 polyploidy	21

± 4.50 cm^3 (mean % resection of 86.34% ± 20.12%). Segmentation by new observer J.J. produced a mean residual enhancing tumor volume of 2.21 ± 3.73 cm^3 (mean % resection of 85.04% ± 23.53%). There were no significant differences in TTR or OS within or between observers (Tables 4 and 5). In summary, absolute residual tumor volumes and overall percentage resections were highly concordant across all observers and time points, further confirming robust intra- and interrater reliability.

Impact of Contrast Enhancement and Resection of Enhancing Tissue on Survival

Figure 3 depicts Kaplan-Meier survival curves showing TTR and OS from the time of initial surgery as they relate to the presence of preoperative contrast enhancement and the volumetric extent of resection of enhancing tissue. Tables 6–8 summarize the results of multivariate analyses examining the survival impact of several clinical or biological variables in addition to contrast enhancement and resection.

On univariate analysis, the presence of contrast enhancement at diagnosis correlated with shorter median TTR (83 vs 169 weeks, p = 0.040) and showed a strong trend toward correlation with shorter OS (196 vs 382 weeks, p = 0.063) (Fig. 3). However, these associations did not hold true on multivariate analysis (Table 6). In enhancing tumors, greater preoperative enhancing tumor volume correlated with shortened TTR on multivariate

TABLE 3: Preoperative and postoperative volumetric data for patients with enhancing tumors

Variable	Value
enhancing WHO Grade II tumors	26/62 (41.94%)
enhancing WHO Grade III tumors	37/38 (97.37%)
tumors w/ astrocytic component & enhancement	34/51 (66.67%)
mean preop contrast-enhancing vol (cm^3)	25.02 ± 27.15
mean postop contrast-enhancing vol (cm^3)	2.36 ± 3.85
mean % resection of enhancing vol	86.26 ± 19.49
no. (%) of pts w/ 100% resection of enhancing vol	16/63 (25.40)
no. (%) of pts w/ >95% resection of enhancing vol	29/63 (46.03)
no. (%) of pts w/ >90% resection of enhancing vol	38/63 (60.32)

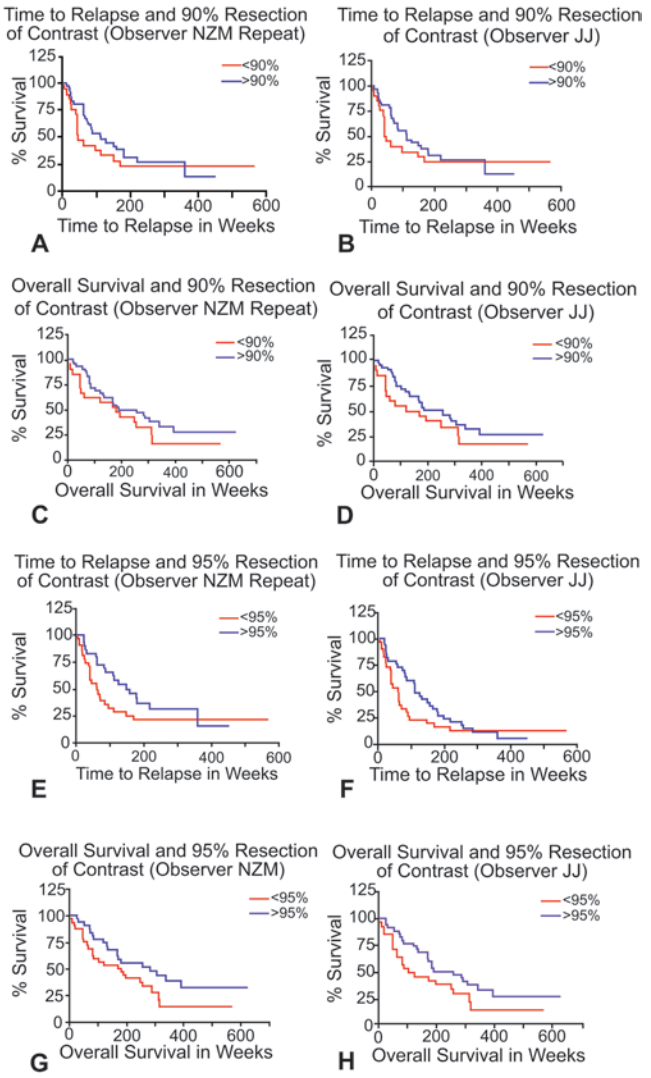

Fig. 2. Kaplan-Meier survival curves of TTR and OS demonstrating repeated measurements to ensure intra- and interrater reliability. All comparisons are made from the time of initial surgery. Both the presence of preoperative contrast enhancement and the volumetric extent of resection of enhancing tissue are considered.

TABLE 4: Median TTR in weeks*

Extent of Resection	TTR (original N.Z.M.)	TTR (N.Z.M. repeat)	TTR (J.J.)
<90%	62	47	45
>90%	111	113	113
log-rank test p value	0.66	0.37	0.38
<95%	64	64	62
>95%	114	154	114
log-rank test p value	0.28	0.080	0.16

* As related to extent of enhancing tumor tissue resection compared between 3 separate observation conditions (original segmentation by author N.Z.M., repeat segmentation by N.Z.M., and segmentation by author J.J.).

analysis (p = 0.00070), suggesting that the burden of enhancing tumor tissue at diagnosis may influence prognosis.

On univariate analysis (Fig. 3), the complete resection of all enhancing tumor tissue was associated with significantly longer TTR (64 vs 174 weeks, p = 0.0082) and OS (135 vs 392 weeks, p = 0.0042). This considerable survival benefit remained significant on multivariate analysis (p = 0.0073 for TTR and p = 0.019 for OS). When the volume of postoperative contrast enhancement was treated as a continuous variable, multivariate analysis showed that a smaller volume of postoperative contrast-enhancing tissue and a larger percentage resection of enhancing tissue correlated with longer OS (p = 0.0012 and p = 0.0041, respectively). Interestingly, when patients in nominal categories were grouped according to the extent of resection of enhancing tumor tissue, neither TTR nor OS increased for patients in whom greater than 90% or even greater than 95% resection of enhancing tissue had been achieved, on either univariate (Tables 4 and 5) or multivariate (Tables 7 and 8) analysis. These results confirm the prognostic importance of maximal—and ideally total—resection of enhancing tissue in oligodendroglial tumors, irrespective of clinical, histological, or other confounders.

Several other variables unrelated to contrast enhancement or resection of enhancing tissue were inversely correlated with survival (Tables 6–8). In particular, increasing age, the presence of an astrocytic component, increasing histological grade, increased Ki 67 labeling

TABLE 5: Median OS in weeks

Extent of Resection	OS (original N.Z.M.)	OS (N.Z.M. repeat)	OS (J.J.)
<90%	121	180	146
>90%	284	223	255
log-rank test p value	0.11	0.22	0.19
<95%	122	175	112
>95%	284	284	257
log-rank test p value	0.090	0.075	0.090

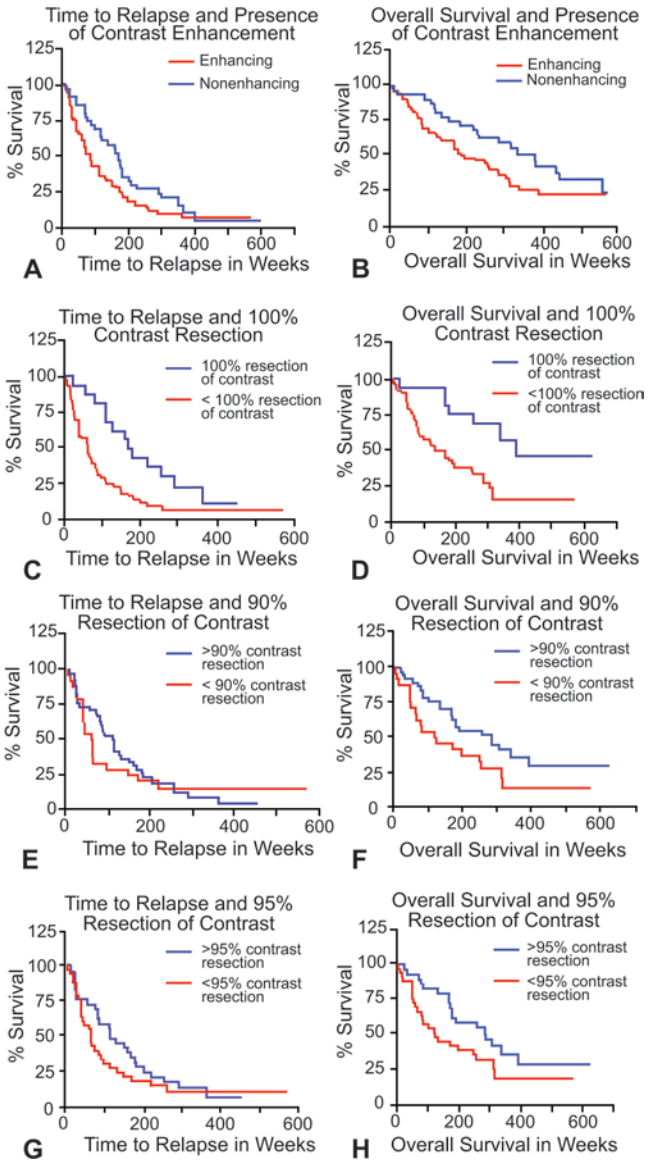

FIG. 3. Kaplan-Meier survival curves of TTR and OS. All comparisons are made from the time of initial surgery. Both the presence of preoperative contrast enhancement and the volumetric extent of resection of enhancing tissue are considered.

index, and absence of del 1p/19q consistently correlated with a worse outcome.

Contrast Enhancement and Genetic Factors

There was no relationship between enhancement status or the volume of contrast enhancement and del 1p/19q or any other genetic markers.

Discussion

This study highlights the importance of contrast enhancement in oligodendroglial tumors based on rigorous, quantitative, volumetric image-processing techniques. Contrary to much of the existing literature, we did not find that the mere presence of contrast enhancement at initial diagnosis was correlated with poorer outcome, although

TABLE 6: Results of multivariate analysis examining the impact of the presence of contrast enhancement on TTR and OS across the entire patient group (n = 100)*

End Point & Variable	p Value	HR
TTR		
preop enhancement	0.49	—
astrocytic component	*0.010*	1.802
WHO Grade III	*0.023*	1.952
cystic	*0.0013*	2.399
OS		
preop enhancement	0.25	—
age	*0.0090*	1.036
WHO Grade III	*<0.00010*	4.626
del 1p/19q	*0.00060*	0.977

* Volumetric variables are shown in bold type. Variables unrelated to enhancement but significantly correlated with TTR or OS are also listed. Italic type indicates statistically significant p values.

a larger initial burden of enhancing tissue was a negative prognostic factor. Our more robust findings relate to resection of contrast-enhancing tumor tissue: In tumors that enhanced, increasing resection of the enhancing portion was independently associated with longer TTR and OS. Importantly, these improved outcomes appeared to be accounted for predominantly by cases in which enhancing tumor tissue was resected completely. The presence of any residual enhancement postoperatively—even less than 5% of the original enhancing volume—left prognosis unimproved. Furthermore, we found no relationship between the presence of del 1p/19q and the presence or volume of contrast enhancement.

The Meaning of Contrast Enhancement

Contrast enhancement of brain tumors on MRI is thought to occur when the blood-brain barrier is disturbed by invasive tumor cells. The breach in the barrier allows the extravasation of gadolinium from within tumor vessels and its subsequent accumulation, which is detectable on T1-weighted sequences.[3,12,37] In a limited number of studies in which biopsies have been obtained from frankly enhancing tumor regions, histological analysis has suggested that enhancing tissue may also represent regions of neovascularity[38] or, perhaps, nodules of increased neoplastic cell density.[37] There is, therefore, some evidence that enhancing tissue represents intratumoral foci with a greater malignant potential, even in the absence of features of frank histological malignancy. It follows that a larger volume of such tissue may increase the risk of tumor recurrence, produce greater resistance to therapy, and eventually lead to a poor outcome. Our findings support this prediction. Although we did not specifically obtain and examine biopsies from contrast-enhancing tumor regions, our results suggest that the presence of enhancing tissue in an oligodendroglial tumor predicts a worse prognosis and that this effect is independent of—instead of rigidly tied to—histological grade. Predictably, we found

TABLE 7: Results of the first multivariate analysis examining the impact of the volume of contrast enhancement on TTR and OS in patients with enhancing tumors (n = 63)*

End Point & Variable	p Value	HR
TTR		
preop enhancing volume	*0.00070*	>1.000
postop enhancing volume	0.17	—
% contrast resection	0.65	—
Ki 67 labeling index	*0.0019*	1.052
del 1p/19q	*0.00030*	0.163
OS		
preop enhancing volume	0.090	—
postop enhancing volume	*0.0012*	0.833
% contrast resection	*0.0041*	0.965
astrocytic component	*0.029*	2.463
MIB-1 >10%	*0.0020*	3.240
Ki 67 labeling index	*0.0016*	1.088
del 1p/19q	*<0.00010*	0.955
early chemotherapy	*0.023*	0.371
late radiotherapy	*0.0041*	0.189

* Volumetric variables are identified in bold type, and were considered as continuous variables in this analysis. Italic text indicates statistically significant p values.

TABLE 8: Results of the second multivariate analysis examining the impact of the volume of contrast enhancement on TTR and OS in patients with enhancing tumors (n = 63)*

End Point & Variable	p Value	HR
TTR		
100% resection of contrast	*0.0073*	0.239
95–99% resection of contrast	0.54	—
90–99% resection of contrast	0.31	—
WHO Grade III	*0.00010*	4.458
del 1p/19q	*0.00070*	0.172
early chemotherapy	*0.028*	0.434
OS		
100% resection of contrast	*0.019*	0.487
95–99% resection of contrast	0.34	—
90–99% resection of contrast	0.23	—
astrocytic component	*0.0087*	2.522
MIB-1 >10%	*0.0064*	2.794
del 1p/19q	*0.00090*	0.972

* Volumetric variables are identified in bold type, and were considered as nominal, categorical variables in this analysis. Variables unrelated to volume of enhancement but significantly correlated with TTR or OS are also listed. Italic type indicates statistically significant p values.

that the overall burden of enhancing tissue on initial diagnosis was directly related to outcome.

Oligodendrogliomas and Resection

Relatively few studies have addressed—either in isolation or as part of a larger study—the prognostic effect of extent of resection of oligodendroglial tumors.[6,8,10,16,17,19,25,28–30,34] The existing studies are all retrospective, and their conclusions are conflicting. Some have reported no statistically significant difference in OS between resection and biopsy groups,[10,17,34] while others have found that the extent of surgery correlated positively with increased survival either independently[6,25,29,30] or when surgery was followed by radiotherapy.[19] As with most studies examining prognostic factors in brain tumors, these studies are weakened by methodological concerns such as small sample size, the combination of pediatric and adult populations despite clearly better prognosis in the pediatric group,[6,19,25,30,34] and a failure to distinguish between histological variants of oligodendroglial tumors (that is, oligodendroglioma vs oligoastrocytoma).[25] Furthermore, none of these studies used reproducible, quantitative volumetric methods. Instead, they relied on highly subjective—and inaccurate—estimates of the extent of tumor resection by individual neurosurgeons (for example, "gross-total resection," "subtotal resection," or "biopsy").

Although our study is also retrospective, it does overcome some of the above methodological shortcomings. First, our study population was a sizable, single-institution cohort of patients who all underwent similar standard imaging and therapeutic regimens and who were followed up for at least 5 years. No pediatric patients were included. Second, we used a standardized, semiautomated method to generate quantitative pre- and postoperative volumetric data from MRI studies. We rigorously ensured objectivity by blinding observers to patient identity and demonstrated good intrarater reliability with our volume measurement methodology. Third, we limited volumetric analysis to enhancing tumors only. Consequently, there were fewer problems dealing with irregular tumor boundaries or peritumoral edema, which can produce inaccuracies in measurements of tumor volumes. Our focused results apply only to a subset of oligodendroglial tumors and hence are more reliable than previously reported findings. To our knowledge, no quantitative volumetric study of resection limited to oligodendrogliomas encompasses both enhancing and nonenhancing tumors. Undertaking such a study would require a consistent and automated method of reliably detecting infiltrative tumor boundaries, possibly by using metabolic imaging (for example, MR spectroscopy)[9,27] or MRI texture analysis techniques.[1]

Contrast Enhancement, del 1p/19q, and Implications for Resection

We found no relationship between the presence or volume of contrast enhancement and characteristic genetic markers of oligodendroglial tumors, particularly del 1p/19q. Some previous studies have looked at imaging correlates of molecular or genetic features in oligodendrogliomas.[2,15,23] Megyesi et al.[23] found that del 1p/19q was associated with an indistinct tumor boundary on T1-weighted MR images, the presence of intratumoral calcification, and paramagnetic susceptibility effect. Similarly, Jenkinson et al.[15] found that an indistinct tumor border and calcification correlated with tumors showing del 1p/19q, but they found no association with paramagnetic susceptibility effect. In both studies, the presence of contrast enhancement was more likely to be associated with a higher tumor grade, but neither study found that contrast enhancement was correlated with del 1p/19q. These results are consistent with our data. Admittedly, our study focused only on contrast enhancement, and we did not examine MR images for other imaging features that might suggest the presence of specific genetic signatures, in large part because we consciously wanted to avoid subjective criteria in our analyses. Nevertheless, recently developed quantitative imaging techniques may allow completely noninvasive detection of del 1p/19q on routine MRI studies with good sensitivity and specificity, potentially obviating the need for molecular diagnostic analysis of actual tumor tissue.[2]

Whether detected in tumor tissue specimens or by noninvasive techniques, the presence of del 1p/19q raises an important clinical dilemma in the context of our own findings. It is known that del 1p/19q is a marker of a relatively benign natural history[14,33] as well as an improved response to chemotherapy.[4,5] Consequently, avoiding or delaying invasive treatments such as aggressive resective surgery, which have the potential to cause neurological morbidity, appears to be an attractive option in patients with del 1p/19q. This is particularly true in young patients with low-grade oligodendrogliomas harboring the genetic signature. Even in older patients or in those with high-grade tumors, it has been argued that del 1p/19q should prompt the early initiation of chemotherapy as the sole treatment modality. In a nonrandomized study of patients with newly diagnosed anaplastic oligodendroglioma, Mikkelsen et al.[24] concluded that patients harboring del 1p/19q can be treated safely and efficaciously with temozolomide alone.

Given this favorable response to up-front chemotherapy, is there a role for resective surgery? Should surgical goals change for enhancing tumors? To date, data have been insufficient to answer these questions. In the study by Mikkelsen et al.,[24] only 11 (22.9%) of 48 patients underwent gross-total resection, and the presence or extent of contrast enhancement was not reported. We believe that 3 key points emerge from our data. First, contrast enhancement is unrelated to del 1p/19q, suggesting that this genetic aberration does not affect tumor vasculature but is instead an intrinsic feature of the tumor cells affecting their response to therapy and/or growth. Second, the presence and volume of contrast enhancement are independent negative prognostic factors. Third, maximal and, if possible, total resection of contrast-enhancing tissue significantly improves prognosis. Clearly, our data support a more aggressive surgical approach to oligodendroglial tumors. Specifically, an attempt should be made to resect all enhancing tissue if safely possible, because doing so is likely to be beneficial regardless of the genetic features of the tumor. To that end, intraoperative or immediate postoperative gadolinium-enhanced MRI, with a clear intent to return to the operative site for additional debulking of

residual enhancing tissue if necessary, may be useful adjuncts. Neuronavigation and awake craniotomy or alternative mapping strategies also may be of use in maximizing removal of enhancing tissue in or near eloquent areas.

Study Limitations

Our study is not without some weaknesses. As mentioned, it is retrospective, and cannot provide Class I evidence to support our conclusions, despite our rigorous volumetric and statistical methods. In addition, no single standardized therapeutic protocol was used across all patients. Consequently, it is possible that over the relatively long follow-up period there were changes in overall treatment patterns (for example, the widespread use of temozolomide in patients treated since 2002). This issue is partially offset by our single-institution patient population managed by a relatively unchanged treatment team over the course of the study. There could also be some concern about the representativeness of the population given the large number of patients that had to be excluded due to inadequate imaging, although there is no reason to think that such patients would be qualitatively different from their counterparts with complete imaging sets. Furthermore, our genetic/molecular analyses did not include an assessment of promoter methylation of the *methyl-guanine methyl transferase (MGMT)* gene, which, like del 1p/19q, may be associated with improved prognosis and responsiveness to chemotherapy with alkylating agents.[26,36]

Any study that uses human observers to generate volumetric data related to tumor size and extent of resection is open to criticisms of bias related to subjective judgments made during the segmentation process. We attempted to validate our volumetric technique by assessing intra- and interrater reliability, which were both found to be satisfactory. Ideally, studies such as ours would employ fully automated tumor segmentation techniques free of the possibility of human bias. While some "fuzzy" algorithms to accomplish this goal have recently been developed, most fully automated tumor classifiers are plagued by systematic errors and significant problems with computational economy.[13] Until these issues are resolved, semiautomated techniques such as we have employed must suffice as an acceptable alternative.

Conclusions

Quantitative MRI volumetric analysis strongly suggests that among enhancing oligodendroglial tumors, the burden of initial contrast-enhancing tumor tissue and the degree of resection of this tissue are related to outcome. These relationships remain significant irrespective of histological grade or molecular genetic classification. Whatever the biological significance of contrast-enhancing tissue is, its complete resection independently and dramatically improves survival. Consequently, resective surgery remains vitally important in the management of patients with these tumors. If possible, surgical planning and intraoperative adjuncts should further the goal of complete resection before adjuvant therapies are initiated.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Preul, Sankar. Acquisition of data: Sankar, Moore, Johnson. Analysis and interpretation of data: Sankar, Moore. Drafting the article: Preul, Sankar, Moore, Scheck, Smith. Critically revising the article: Preul, Sankar. Statistical analysis: Sankar, Moore. Administrative/technical/material support: Preul, Ashby, Shapiro, Smith, Spetzler. Study supervision: Preul, Sankar.

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