Growth Kinetics and Treatment Response of the Intracerebral Rat 9L Brain Tumor Model: A Quantitative in Vivo Study Using Magnetic Resonance Imaging

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ABSTRACT
We report the use of magnetic resonance imaging (MRI) for in situ tumor growth rate studies of experimental intracranial 9L tumors. \( T_T \)-weighted spin-echo coronal magnetic resonance images of rat brains with 9L tumors were obtained every 2 days beginning at 8–11 days postimplantation using a 7 tesla MRI system. Tumors were clearly delineated in the images as a hyperintense region with a relatively well-demarcated border and minimal peritumoral edema. Tumor volumes from individual slices were summed together to yield the total tumor volume. The accuracy of this methodology for volumetric determination was verified by MRI phantom studies. Tumor growth rates determined from sequential MRI measurements of tumor volumes were quantitated in terms of volumetric doubling time. Tumor doubling times were found to range from 50 to 81 h, with an average of 66 ± 8 h (n = 10). Intracranial 9L tumors were found to grow exponentially over the entire life span of the animal, allowing treated animals to serve as their own control if the \( T_T \) was determined from three to four MRI scans before treatment administration. The intracerebral tumor growth delay following a single injection of 1,3-bis(2-chloroethyl)-1-nitrosourea (13.3 mg/kg, i.p.) allowed for noninvasive determination of in vivo log cell kill. A 2.0 ± 0.2 (n = 3) log cell kill from 1,3-bis(2-chloroethyl)-1-nitrosourea treatment was found from posttreatment MRI volume measurements. These results demonstrate that MRI provides a powerful and sensitive method for assessing the growth and treatment response of intracranial 9L tumors in the rat.

INTRODUCTION
Malignant gliomas constitute a major therapeutic problem because of their frequency of occurrence and extremely poor prognosis. Rodent brain tumor models play an important role in the in vivo evaluation of novel therapeutic approaches (1). The therapeutic response of orthotopic brain tumors has traditionally been quantitated using animal survival, tumor weights following excision, or colony-forming assays of cells cultured from the in situ tumor as biological end points (2–12). These methods have proved valuable for in vivo testing of new therapeutic approaches but suffer the disadvantage that large numbers of animals are typically required due to the variable growth rate and therapeutic response. A method that would allow the intracranial tumor volume to be noninvasively and repeatedly monitored over the life span of individual animals would be beneficial for the evaluation of new therapeutic approaches. In this study, we evaluated the use of MRI as a noninvasive tool to serially monitor the growth and therapeutic response of the intracranial rat 9L brain tumor model (2, 5). Tumor volumetric measurements by MRI were validated using phantoms of known volumes. We report that \( T_T \) of intracranial 9L tumors could be accurately obtained in individual rats from serial MR images. Significant animal to animal variation in tumor growth rates using this approach was observed; however, all untreated 9L tumors were found to grow exponentially over the entire life span of the animal. The exponential growth characteristic allowed for treated animals to serve as their own control if the \( T_T \) was determined from several MRI scans before administration of treatment. A marked decrease in growth rate was observed following BCNU administration, and cell kill was determined for individual animals from tumor volume growth delay measurements. Furthermore, changes in tumor morphology following BCNU treatment could be detected as regional changes in image signal intensity. This study shows the usefulness of MRI as a powerful noninvasive tool for evaluating treatment of in vivo intracranial brain tumor models.

MATERIALS AND METHODS
Cell Culture Conditions. 9L tumor cells were grown as monolayers in 75-cm\(^2\) sterile plastic flasks in modified Eagle’s MEM with 10% FCS. Cells were cultured in an incubator at 37°C in an atmosphere containing 95% air and 5% CO\(_2\) until confluent. Cells were harvested by trypsinization, counted, and resuspended in serum-free media for intracerebral injection.

Induction of Brain Tumors. 9L tumor cells were implanted in anesthetized (ketamine, 87 mg/kg, + xylazine, 13 mg/kg)...
mg/kg body weight i.p.) adult male Fischer 344 rats weighing between 125 and 150 g. A small skin incision over the right hemisphere was made. A high-speed drill was used to create a 1-mm diameter burr hole through the skull. The burr hole was filled with bone wax to minimize the potential for extracerebral extension of the tumor tissue. The skin was sutured together and the rats were allowed to recover.

**MRI.** All in vivo MRI experiments were performed on a SISCO system equipped with a 7.0 tesla, 18.3-cm horizontal bore magnet (300-MHz proton frequency). For MRI examination, rats were anesthetized with either sodium pentobarbital (65 mg/kg i.p.) or a ketamine/xylazine (87 mg/kg/13 mg/kg i.p.) mixture and maintained at 37°C inside the magnet using a heated circulating water blanket. MRI of rat brains was initiated between 8 and 11 days following cell implantation and repeated every other day. The rat head was positioned inside a 4-cm diameter birdcage rf coil which was designed and constructed with ear bars to secure the position of the head during the acquisition. For each MRI session, a single-slice gradient-recalled-echo image was acquired with 1-mm "saturation cross-hairs" imprinted on the axial and coronal images to facilitate rapid and reproducible positioning of the animal. Multislice axial images were acquired using a standard spin echo sequence. T2-weighted images through the rat brain were produced using the following parameters: TR/TE = 3500/60, FOV = 30 × 30 mm using a 128 × 128 matrix, slice thickness = 0.5 mm and slice separation = 0.8 mm. Twenty-five slices were acquired followed by acquisition of a second set of 25 slices with a slice offset of 0.4 mm providing contiguous image data set of the rat brain.

**Tumor Treatment.** BCNU was obtained from the University of Michigan Hospital pharmacy and dissolved in absolute ethanol and diluted in saline (0.9% NaCl) to a final concentration of 3.3 mg/ml in 10% ethanol. Each treated animal (n = 3) received a single LD50 injection of BCNU (13.3 mg/kg i.p.) after three or four pretreatment tumor MRI volumetric measurements. This procedure allowed each animal to serve as its own control because the Td could be accurately determined from as few as three pretreated volumetric measurements.

Certain anesthetics have been reported to induce changes in liver enzymes accelerating the clearance of BCNU. For example, chronic p.o. administration of phenobarbital has been shown to completely eliminate the antitumor activity of BCNU against the rat intracranial 9L tumor model (13). Because the use of anesthetics was necessary to keep the animals motionless during MRI examination, their effects on induction of liver enzymes was minimized in two ways: (a) only the ketamine mixture was used (rather than pentobarbital) for treatment studies since it has been shown to have limited potential for long term induction of liver enzymes (14), and (b) following acquisition of the first two or three MRI scans 2 days apart, 3 days were allowed to pass between the last time the animal was anesthetized and BCNU administration. This was done to allow for clearance of the anesthetic and reversal of the potential changes in liver enzyme levels. On the third day following the last MRI scan, BCNU was administered to unanesthetized rats. Within 1–2 h following BCNU administration, MRI scanning was resumed and continued every 2–3 days until death. Pretreatment Td was determined from the initial three or four MRI scans which allowed for sufficient time to follow treatment response before death.

**Calibration of MRI Volume Measurements.** Calibration of MRI volume measurements was achieved by measuring the volume of four different sphere phantoms using the same MRI acquisition protocol used for scanning rats. The phantoms consisted of spherical glass bulbs (Wilmad Glass Co., Buena, NJ). The "actual volumes" of the phantoms, calibrated using a Hamilton syringe, were 22.5, 31.2, 113.5, and 297.7 mm3. Phantom volumes were quantitated from MRI data sets using a region of interest program provided with the SISCO software and were compared with the actual volume of each phantom to determine the accuracy of the MRI method. For all MRI phantom validation experiments, phantoms were filled with cupric sulfate (20 mM) and submerged in a bottle filled with distilled water.

Partial volume effects, assuming square slice profiles and ideal spherical volumes, were modeled to define the precision of this methodology. MRI volumes were determined by summing all of the cylinders that spanned the object. Errors arising from partial volume effects result in maximum overestimation of experimental volume if voxels are included in the volume when any fraction of a voxel is within the sphere. Conversely, if only voxels entirely within the sphere are included, then an underestimated volume results. An intermediary condition is where the center of each slice profile circumscribes the projected area of the sphere for that slice. Modeled volumes and associated partial volume errors were estimated using four idealized spheres having the same volume as the phantoms.

**Quantification of Intracranial Tumor Volumes.** For volume measurements at each time point, the area (volume) of tumor visualized in each slice was manually outlined using a region of interest program provided with the SISCO MRI software. The outlined tumor area in each cross-sectional image was multiplied by the slice separation (0.4 mm) to calculate the tumor volume in each slice. The tumor volumes of individual slices were summed to yield the total volume of the tumor. Although tumors as small as 2 mm3 (about 2 mm in diameter) were measured using MRI, tumors with a minimal volume of 8–10 mm3 were used for the initial volumetric time point since there was less uncertainty in the accuracy of the initial tumor volume measurement.

**Determination of Tumor Td and Log Cell Kill.** Tumor volumes measured by MRI were plotted against hours postimplantation to determine the growth rate of the intracranial 9L tumors. By using the definition of exponential growth,

\[ V(t) = V_0 \cdot 10^{kt} \]  

where \( V(t) \) is tumor volume at time \( t \), \( V_0 \) is the initial tumor volume, and the volumetric \( Td \) was calculated from the expression, \( Td = (\log 2)/k \). The tumor growth rate constant \( k \) was obtained from an exponential curve fit of the volume data points using a least-squares algorithm.

In principle, cell kill for each treated animal can be determined by using the expression for posttreatment tumor volume \( V_p \).

\[ V_p(t) = [(1 - f_i) \cdot V(t) \cdot e^{(-u - m)}] + f_i \cdot V(t) \]  

\[ \]
where $V(t_f)$ is tumor volume at the time of treatment ($t_f$), $f_k$ is the fraction of cells killed by the treatment, and $k$ is the posttreatment growth rate constant. The first term in Equation B describes the growing fraction following treatment while the second term describes the dead cell fraction following treatment. In this study, Equation B was used to model the effect of increasing cell kill on the posttreatment tumor growth rate.

Given the empirical growth delay, $(T_i - T_f)$ which is defined as the difference in time for untreated ($T_i$) and treated ($T_f$) tumors to grow to the same size (15), cell kill can be estimated by

$$\log(\text{cell kill}) = (T_i - T_f)k \quad (C)$$

The values of $T_i$, $T_f$, and $k$ can all be accurately determined from the serial MR images of the intracranial tumor, thus Equation B was used to determine the cell kill for animals treated with BCNU in this study.

**RESULTS**

**Accuracy of MRI Volume Measurements.** Shown in Fig. 1 are the “actual” phantom volumes (obtained by measurements using a Hamilton syringe) plotted against volumes determined by MRI. All discrepancies from the unity line were within 10%. Modeled extrema of partial volume errors ranged from $\pm 21\%$ (smallest phantom) to $\pm 9\%$ (largest phantom). Close agreement between MRI and actual phantom volumes suggests that the MRI methodology is accurate and well within predicted precision limits set by partial volume models.

**Quantitation of $T_d$ from MR Images of Rat Intracranial Tumors.** Intracranial 9L tumor volumes could be measured by MRI approximately 10 days postimplantation. Shown in Fig. 2 is a representative series of T2-weighted coronal MR images revealing the growth of an untreated intracranial tumor from 12 to 22 days postimplantation. During this time period, the tumor volume increased from 23 to 263 mm$^3$. In Fig. 2, the series of MR images are shown from the same region of the rat brain located at approximately the largest diameter of the tumor. The tumor is clearly evident in the right hemisphere as a hyperintense region which is easily distinguished from the normal brain parenchyma. An increasing mass effect with time, due to the presence of the expanding tumor, is evident (e.g., midline shift). The characteristic features of untreated 9L tumors imaged in this study were a well-demarcated tumor mass with a relatively uniform hyperintense tumor signal and minimal peritumoral edema. The small and disseminated hypointense regions apparent in the tumors in Fig. 2 are believed to arise from paramagnetic susceptibility differences within the tumor mass, which are accentuated at the relatively high magnetic field (7 tesla) used in this study, and were included in tumor volume calculations. Recent studies of excised tissue samples have revealed that the brain adjacent to the 9L tumor in the ipsilateral hemisphere had no significant change in water content (edema) relative to the contralateral hemisphere.\(^4\)

Shown in Fig. 3 is a semi-log plot of the volume versus hours after intracerebral implantation of $10^5$ 9L tumor cells from the rat shown in Fig. 2. The individual points are shown along with the line representing the least-squares fit. The $T_d$ of the 9L tumor shown in Fig. 3 was determined to be 68 h. This plot reveals the typical exponential growth pattern seen for all untreated intracerebral 9L tumors. Untreated intracranial tumor $T_{dcs}$ are listed in Table 1 along with survival times and the final tumor volumes. The mean tumor $T_d$ of intracranial 9L tumors determined from sequential MRI measurements was $66 \pm 8$ h ($n = 10$, $\pm$ SD). All untreated intracerebral 9L tumors imaged in this study were found to grow exponentially over the entire life span of the animal, with an average correlation coefficient of 0.986 ± 0.14 ($n = 10$, $\pm$ SD). The final average tumor volume obtained at or near death was $223 \pm 53$ mm$^3$ ($n = 7$, $\pm$ SD).

**Quantitation of Therapeutic Efficacy from MRI Tumor Volumetric Measurements.** Assuming an intracranial tumor with a $T_d$ of 50 h, a theoretical growth curve was generated using Equation A as shown in Fig. 4. Log kill values of 0.2, 0.4, 0.7, 1, 2, and 3 were used in Equation B to model the effect on the initial tumor growth as shown in Fig. 4, b-g, respectively. This model assumes that on the day of treatment, the growth rate constant ($k$) for the surviving cells remains the same average rate as that of untreated cells, cells rendered nonviable by the treatment do not undergo further division, and the volume of the displaced brain does not shrink, even following significant cell killing (e.g., $3 \times$ log kill), but rather is replaced with reactive astrocytosis, necrosis, etc. The growth delays for 0.2, 0.4, 0.7, 1, 2, and 3 log kill, given a $T_d$ of 50 h, were calculated to be 33, 66, 116, 166, 332, and 498 h, respectively, as shown in Fig. 4, b-g.

In order to determine the sensitivity at which the MRI volumetric measurements could detect a change in $T_d$ (or cell kill), all of the untreated rats were analyzed as if they were treated in the following manner. The first four volumetric measurements of each untreated 9L tumor were used to determine the value of $k$ for that particular tumor. The fourth

\[^4\] R. F. Keep, personal communication.
Fig. 2 A series of coronal T2-weighted MR images of a rat brain (Rat 2, Table 1) with time after implantation of $10^9$ 9L tumor cells. Each displayed image is from approximately the same region of the brain. Clearly evident in the right hemisphere is a hyperintense region corresponding to the 9L tumor mass. Untreated tumor volumes for each time point are as follows [day postimplantation/tumor volume (mm$^3$)]: $a$, 12/23; $b$, 14/40; $c$, 16/64; $d$, 18/97; $e$, 20/171; and $f$, 22/263.

volumetric data point (the volume at the supposed time of treatment) was used with the subsequent volume measurements along with $k$ (determined from pretreatment volumetric data) to calculate the cell kill ($f_c$) using an iterative fitting algorithm for Equation B. Analyzing the data in this manner revealed that for all untreated rats, cell kill values ranged from $-0.1$ to $+0.1$ log cell kill. Thus, evaluation of MRI tumor growth data from untreated rats indicated that this MRI approach was sensitive enough to detect changes in tumor growth rates when the treatment resulted in $>0.1$ log kill.

**Therapeutic Efficacy of BCNU on Intracranial 9L Tumors.** Fig. 5 shows a semi-log plot of the volume versus time postimplantation of an intracranial 9L tumor. At approximately 1–2 h before the third volume measurement, the rat was treated with a LD$_{10}$ of BCNU. The time course of posttreatment tumor volumes shows a deviation from the well-defined pretreatment exponential growth curve. The volume of the tumor appears to increase (although the rate of growth is attenuated) for 5 to 6 days after treatment followed by a decrease in tumor volume during 6–14 days posttreatment. The first and last three data points in Fig. 5 were used to determine the pretreatment and post-treatment tumor $T_d$, respectively. After approximately 14 days posttreatment (672 h postimplantation in Fig. 5), the $T_d$ of the intracranial 9L tumor was 49 h, nearly identical to the pretreatment rate of 51 h. A growth delay of 356 h (≈15 days) was calculated from the MRI data and when combined with the pretreatment growth rate constant ($k$) of 50 h, a log kill of 2.1 was calculated using Equation C. This calculation compares favorably with the modeled cell kill plot shown in Fig. 4 which used a pretreatment $T_d$ of 50 h, comparable to the rat shown in Fig. 5. Log kills of 2.1 and 1.8 were found for the other two rats treated with BCNU. An average survival time of 38 ± 5 days ($n = 3$, ±SD) for BCNU-treated rats was found compared to the average survival time of 22 ± 2 days (Table 1) for untreated animals yielding a 73% increased life span for BCNU-treated animals.

The use of MRI also allowed for monitoring, noninvasively, the changes in tumor morphology following treatment. Fig. 6A-F displays the coronal T2-weighted MR images of the same 9L tumor shown in Fig. 5 at Days 14, 17, 20, 24, 26, and 28 postimplantation, respectively. Two h prior to acquiring the 14-day image (Fig. 6a), the rat was treated with a single dose of BCNU (13.3 mg/kg i.p.). The tumor continued to expand until Day 20 postimplantation (Fig. 6c) and a heterogeneous reduction in tumor image intensity was noted at later times following treatment (Fig. 6, d-f).

**Calculation of the Cell Loss Factor.** In a previous study of intracranial 9L tumors, the $T_{pos}$, the time required for a tumor to double its size in the absence of cell loss, was determined to be 64.2 h using double labeling with iododeoxyuridine and bromodeoxyuridine (16). This value of $T_{pos}$ combined with our average value of $T_d$ for untreated 9L tumors (66 h), allowed the cell loss factor ($f$) to be determined using Equation D below as described previously (17).

\[ f = 1 - \frac{T_{pos}}{T_d} \] (D)
DISCUSSION

Quantitation of the in vivo antitumor activity of an experimental treatment is an essential component of assessing new therapeutic approaches. Traditional survival studies using animal brain tumor models, although invaluable, require a greater than one log kill to discern a statistically significant increase in life span (3). MRI of intracranial rodent brain tumor models offers a more sensitive indicator of therapeutic effectiveness since a >0.1 log kill can be detected in a single animal from serial MR images and should facilitate an earlier interpretation of brain tumor responsiveness relative to survival studies. Furthermore, studies of intracranial tumor models using MRI should help to improve our understanding of the biochemical or physiological basis of nonresponsiveness due to such variable factors as growth rate, size, location, and vascularity. This approach should also help to increase the throughput of evalu-
Fig. 6  Coronal T2-weighted MR images of a rat brain (same rat as in Fig. 5) with time after implantation of 9L tumor cells. Each displayed image is from approximately the same region of the brain. a–f, 9L tumor brain at Days 14, 17, 20, 24, 26, and 28 postimplantation, respectively. Two h prior to acquiring the 14-day image (a), the rat was treated with a single dose of BCNU (13.3 mg/kg i.p.). The tumor continued to expand until Day 20 postimplantation and a heterogeneous reduction in tumor image intensity was noted at later times following treatment (d–f).

atiing novel therapeutic approaches for treating brain tumors, since an individual animal can serve as its own control due to the exponential growth characteristic of this tumor model.

The exponential growth of the intracranial 9L tumor is consistent with a model in which the cell cycle time, growth fraction, and rate of cell loss are all constant with time (17). The nearly zero cell loss factor (2.7%) also agrees well with our histopathological observation of minimal necrosis within untreated intracerebral 9L tumors. It should be noted, however, that the biological characteristics of the 9L tumor may vary from institution to institution and that the potential, obtained from the literature (16) may not exactly represent the potential for the 9L tumors studied in our laboratory. In the present study, we used a single dose of BCNU to demonstrate the feasibility of monitoring therapeutic-induced tumor growth inhibition using MRI. This approach should provide a unique opportunity to evaluate various therapeutic interventions such as systemically or intratumorally administered chemotherapeutic agents, radiation, interstitial implants of drugs encapsulated in biodegradable polymers, and after transfer of a therapeutic gene construct. Application of this latter approach to MRI is appealing since the vector or virus is typically delivered by a direct injection into the tumor mass. Prior knowledge of the size, location, and pretreatment growth rate of an individual intracerebral tumor would allow individualization of the dose, provide coordinates for stereotaxic delivery, and monitoring of the therapeutic response. It should also be possible to use MRI to study other brain tumor models such as heterologous transplantation of human brain tumors in athymic nude mice and nude rats, although for each model, the untreated growth characteristics must be established.

The range in $T_d$ of intracerebral 9L tumors (from 50 to 81 h) found in this present study (Table 1) provides a direct observation of the heterogeneity of tumor growth rates in this brain tumor model system. We found that the variation in tumor growth rates is inherent to the biological system since it is present in a group of animals implanted on the same day with the same cell suspension. This observation helps to elucidate the reason for the marked variability in tumor sizes reported in studies using excision and weighing of the tumor (see Fig. 2 in Ref. 5).

Although the $T_d$ dramatically decreased following treatment with BCNU, the tumor volume still increased for 4 to 5 days posttreatment before the tumor volume began to shrink (Fig. 5). This phenomenon is most likely due to BCNU rendering many cells nonviable immediately following treatment. However, some of these cells probably divide several times before death. The cells remaining viable following treatment grow at the same average rate as untreated cells, resulting in the regrowth observed at Day 14 posttreatment in Fig. 5. This time course is nearly identical to that previously reported for changes in tumor weight following a LD$_{10}$ of BCNU (5) and for the removal of dead tumor tissue from the brain of a rat (18). The theoretical growth delay curves shown in Fig. 4 serve to provide an approximation of the growth delay expected from a given log kill. We did not attempt to model the more complex tumor volume time course observed following BCNU treatment since log kill can be estimated from the tumor growth delay (5). A more complete model would require additional functions describing such phenomenon as the swelling of cells following death (18), the ability of treated cells to divide a few times after treatment (19), and the removal of dead cells from the brain (18). However, Equation B can be used to model the changes in tumor growth for lower cell kills (0.2-1.0 log kill) in which the swelling of cells and cell removal would not produce the profound changes seen with log kill in the range of 2.0-3.0.

The mean 2.1 ± 0.2 log kill observed in the present study using MRI was lower than the mean log kill of 3.23 ± 0.57 (SD, $n = 57$) previously reported for a LD$_{10}$ of BCNU, measured
using the colony-forming efficiency assay (5). Our lower cell kill could be due to several factors such as a residual anesthetic-induced increase in liver enzymes involved in BCNU removal or differences in the time between preparation of the BCNU solution and administration since BCNU in aqueous solution is unstable (20). Many other biological factors could also be responsible for the difference between the cell kill value calculated from the MRI data and the value determined by colony formation assays. For example, the host cell composition of the tumor will vary significantly after treatment, thereby influencing cell kill estimates made from volume measurements (21). The cell loss factor will increase dramatically after treatment and will be variable during the posttreatment period and intratumoral edema and necrosis may also be complicating features. Furthermore, results obtained from excision assays have been reported to not always correlate with studies using in situ assays in which the tumor is allowed to remain intact in the animal (22, 23). Finally, the large variability in cell kill measured by the colony-forming assay (1–1.5 logs) and the biological factors which contribute to volume but not to tumor cell colony formation indicate that the MRI measurements of BCNU-treated animals are consistent with the expected cell kill from a single dose of BCNU.

The validity of MRI volume measurements has been established by direct comparison with either histological volume measurements (24) or volumes of excised tumors (25). MRI volume measurements have also been reported to estimate intracranial tumor progression (26) and assess the average treatment response of hepatic metastases of colon cancer in rats (27). For most MR images, partial volume effects from limited resolution blur even high-contrast tumor borders. Consequently, tracing the shape of interest may result in errors in accurate volume measurements. This potential source of error, as well as geometric accuracy of the imaging system, was evaluated by the use of phantoms of predetermined volumes. With a 0.5-mm slice sampling, the partial volume effect was determined to be minimal, thus verifying the accuracy of the tumor volume measurements by the present method. Furthermore, we also evaluated the effects of administration of contrast agent (gadolinium diethylenetriamine pentaacetic acid) on the delineation of 9L tumor boundaries using T1-weighted images. Tumor volumes calculated from T2- and T1-weighted contrast enhanced images were found to be nearly identical to the T1-weighted image data set yielding tumor volumes of approximately 10% larger. This larger volume was presumably due to "leakage" of the contrast agent from the tumor into the adjacent normal brain parenchyma. Contrast enhancement for delineation of the 9L tumor border resulted in an overestimation of tumor volume and is therefore not advised for determining tumor volumes from MR images since this tumor model characteristically has well-demarcated tumor boundaries with minimal peritumoral edema.

Finally, because MRS provides a method for in vivo monitoring of various tumor metabolites and pH (28), there has been great interest in determining whether specific changes in metabolite levels following treatment are predictive of therapeutic outcome. Studies of experimental intracerebral brain tumors using 31P, 13C, and 1H MRS have been reported (29–32). Since MRI can now be used to quantitate treatment effectiveness in an individual animal, correlative studies between MRS and MRI using animal brain tumor models should provide an exciting opportunity to evaluate MRS as a predictor of therapeutic efficacy. This type of correlative study would serve to more clearly define the use of MRS for evaluating brain tumor treatment in the clinical setting.

ACKNOWLEDGMENTS

The 9L gliosarcoma cell line was kindly provided by the Brain Tumor Research Center at the University of California, San Francisco. We thank Christina Hurlbert for excellent technical assistance and Reviewer 2 for helpful comments.

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