ABSTRACT
The effects of chemotherapy [25 mg/kg, 1,3-bis(2-chloroethyl)-1-nitrosourea administered with a single i.p. injection] on cellular energetics by 31P nuclear magnetic resonance (NMR) spectroscopy, total tissue sodium by single-quantum (SQ) 23Na NMR spectroscopy, and intracellular sodium by triple-quantum-filtered (TQF) 23Na NMR spectroscopy were studied in the s.c. 9L glioma. Animals were studied by NMR 2 days before therapy and 1 and 5 days after therapy. Destructive chemical analysis was also performed 5 days after therapy to validate the origin of changes in SQ and TQF 23Na signals. One day after treatment, there was no significant difference between control and treated tumors in terms of tumor size or 23Na and 31P spectral data. Five days after therapy, treated tumors had 21 ± 8% (P < 0.05) lower SQ 23Na signal intensity, 46 ± 20% (P < 0.05) lower TQF 23Na signal intensity, 125 ± 51% (P < 0.05) higher ATP:Pi ratio, 186 ± 69% (P < 0.05) higher phosphocreatine:Pi ratio, and 0.17 ± 0.06 pH units (P < 0.05) higher intracellular pH compared with control tumors. No significant differences in TQF 23Na relaxation times were seen between control and treated tumors at any time point. Destructive chemical analysis showed that the relative extracellular space of control and treated tumors was identical, but the treated tumors had 21 ± 8% (P < 0.05) lower total tissue Na+ concentration and 60 ± 24% (P < 0.05) lower intracellular Na+ concentration compared with the controls. The higher phosphocreatine:Pi and ATP:Pi ratios after 1,3-bis(2-chloroethyl)-1-nitrosourea treatment indicate improved bioenergetic status in the surviving tumor cells. The decrease in SQ and multiple-quantum-filtered 23Na signal intensity was largely attributable to a decrease in Na+, because the treatment did not change the relative extracellular space. The improved energy metabolism could decrease the intracellular concentration of Na+ by increasing the activity of Na+-K+-ATPase and decreasing the activity of Na+/H+. Although both 23Na and 31P spectra were consistent with improved cellular metabolism in treated tumors, the 23Na methods may be better suited for monitoring response to therapy because of higher signal/noise ratio and ease of imaging the single 23Na resonance.

INTRODUCTION
Most normal cells maintain an Na+ concentration of ~10 mEq/L against an Na+ concentration of 150 mEq/L. This transmembrane sodium gradient is maintained by the action of the Na+/K+-ATPase and is used to drive several vital cellular processes through the action of membrane-bound exchangers and cotransporters. For instance, pH, is regulated to a large extent by a Na+-H+ exchanger that pumps excess H+ ions out of the cell by allowing Na+ ions into the cell. In addition, a Na+-glucose cotransporter is used to move glucose molecules into the cell.

The transmembrane sodium gradient may be disrupted in many disease states, including cancer (1–4). Measurement of Na+ in tumors may be useful to monitor therapy because Na+ is sensitive to changes in cellular metabolism, such as ATP availability and intracellular acid production. 23Na NMR provides a convenient, relatively sensitive, nondestructive method for detecting Na+ in biological tissue and has been the focus of numerous recent imaging studies in humans (5, 6). However, Na+ exists in only one chemical form in tissue; consequently, its signals from the intra- and extracellular compartments are coincident. Shift reagents, such as TmDOTP5, have been developed to separate the intra- and extracellular sodium in tissues of intact animals (7, 8). These compounds, however, are by necessity anionic and bind competitively with all biological cations. They could unintentionally compromise the animal physiology by disrupting normal Ca2+, Mg2+, Na+, or K+ ion gradients. Therefore, shift reagents have not yet been used in chronic experiments.

MQF 23Na NMR spectroscopy has been proposed as an alternative means to partially discriminate between intra- and extracellular Na+ (9). Because MQF techniques rely only on differences in relaxation properties of Na+ and Na+, they can be used to study the same tissue repeatedly over an extended period of time. The presence of an Na+ component in double-quantum-filtered and TQF signals has been demonstrated in several animal models and perfused organ experiments (10, 11). This extracellular component, however, is much less than the extracellular component of the SQ 23Na signal and is relatively insensitive to changes in Na+ content (11, 12). Thus, the MQF signals can be useful for monitoring changes in Na+.

Several studies have shown that untreated tumor growth is accompanied by a progressive decline in bioenergetic status, i.e., decreases in PCr and ATP levels and increased levels of Pi (13–16). Because these changes resemble the effects of ischemia, it has been suggested that the tumor suffers from hypoxia as it outgrows its blood supply (17, 18). Several researchers have also investigated the effects of various therapies on tumor bioenergetic status. Hyperthermia, photodynamic therapy, and some forms of chemotherapy (treatment with tumor necrosis factor, for example) cause reduced levels of ATP and increased Pi (19). This observation is consistent with severe ischemia. On the other hand, radiotherapy and most chemotherapy cause increased ATP and PCr levels and decreased Pi (20–22). This effect, termed “tumor activation,” is thought to be a result of increased perfusion and oxygenation of the tumor (23).

Previous 31P NMR studies have shown that chemotherapy of 9L glioma by BCNU increases the high energy phosphates relative to Pi (24–27). The mechanism for this paradoxical phenomenon of metabolic activation after treatment is not entirely clear, but it is likely to be related, at least in part, to tumor reoxygenation (19, 23, 27). Tumor reoxygenation after therapy has been attributed to several factors: the death of some tumor cells may reduce total oxygen consumption; removal of dead cells may lessen the average intercapillary distance;
tumor interstitial pressure may decrease, so that fewer tumor vessels are occluded, or an increase in vascularization may occur (23). The increased ATP levels associated with this treatment should increase Na\(^+/K^+\)-ATPase activity. On the other hand, the Na\(^+\)-H\(^+\) exchanger activity should decrease because of reduced intracellular acid production from glycolysis. These two effects should reduce Na\(^+\)_tumor in tumors subjected to chemotherapy. The aim of this study was to determine whether changes in cellular metabolism, as detected by \(^{31}\)P NMR, correlate with changes in Na\(^+\)_total and Na\(^+\)_tumor levels, as detected by SQ and TQF \(^{23}\)Na NMR, respectively. Destructive chemical analysis was also performed to determine the origin of changes in SQ and TQF \(^{23}\)Na NMR signals.

MATERIALS AND METHODS

**Tumor Cell Culture.** 9L tumors were maintained in cell culture in McCoy’s 5a supplemented with FCS (5–10%) and 20 mM HEPES, at pH 7.4. Cells were maintained in experimental growth by routine passage, twice weekly. New cultures were started from frozen stocks every 3 months. Tumors were started by trypsinizing cultures, stopping the trypsin with spent medium and centrifuging at 2000 \( \times \) g for 2 min at 4°C. Spent medium was decanted, and the cell pellets were rinsed in PBS, pH 7.4. Cells were concentrated to 10^6/ml in PBS.

**Rat Tumor Model.** All animal protocols were approved by the University Laboratory Animal Research Committee of The University of Pennsylvania. Male Fisher 344 rats (70–90 g) were anesthetized by an i.p. injection of 0.05 ml of ketamine (91 mg/ml) and acepromazine (0.91 mg/ml). The animal’s flank was shaved, and a 10–15 mm diameter tumor was surgically removed. A small glass bulb was used for tumor interstitial pressure measurement and to correct for non-zero noise introduced by the magnitude calculation procedure. The SQ and TQF \(^{23}\)Na signals arising from the tumor were referenced to the SQ \(^{23}\)Na signal from the glass bulb. As shown in Fig. 1B, the TQF signal areas were plotted against preparation times and fit to a biexponential curve to determine the fast and slow transverse relaxation times (\(T_2f\) and \(T_2s\), respectively) and longitudinal magnetization. \(^{13}\)P resonance areas were determined by spectral curve fitting after application of 35 Hz linebroadening and Fourier transformation using Nuts. No corrections were applied for saturation effects, because they are negligible for ATP and small for Pi and PCr (30). The area of the \(\beta\)-ATP resonance was used to calculate ATP:P ratio, because it contains minimal contributions from other compounds (7). Intracellular pH was calculated from the chemical shift of Pi relative to PCr using the equation (31):

\[
\text{pH}_i = 6.75 + \log \left( \frac{\delta_{\gamma,\text{PCr}} - 3.28}{5.69 - \delta_{\gamma,\text{PCr}}} \right)
\]

**Destructive Chemical Analysis.** The effects of chemotherapy on rECS, [Na\(^+\)]_tumor, and [Na\(^+\)]_tumor were measured by destructive chemical analysis to determine the origin of changes in the SQ and TQF \(^{23}\)Na spectra. Bench experiments were performed 5 days after therapy in age- and weight-matched animals bearing size-matched 9L tumors. Half of the animals received 25 mg/kg BCNU \((n = 7)\), whereas the others received the sham solution \((n = 7)\). As in the NMR experiments, the animals were anesthetized and placed on a water recirculating heating pad. A carotid artery was cannulated and connected to a pressure transducer (Ohmeda Medical Devices, Madison, WI) to measure blood pressure transducer (Ohmeda Medical Devices, Madison, WI) to measure
pulse pressure and heart rate on a digital blood pressure monitor (Columbia Instruments, Columbus, OH).

A 40 mm solution of TmDOTP\textsuperscript{3-}, a \textsuperscript{23}Na shift reagent and extracellular space marker (8, 32) purchased from Macrocyclics, Inc. (Richardson, TX), was infused through a catheter in the jugular vein using an infusion pump (Harvard Apparatus, South Natick, MA). A previously established infusion protocol was followed that allowed the TmDOTP\textsuperscript{3-} to equilibrate throughout all extracellular spaces (8). A blood sample (~0.5 ml) was withdrawn from the arterial line, and the tumor was quickly excised, removing all surrounding skin and muscle. The tumor was immediately freeze-clamped using aluminum tongs precooled in liquid nitrogen, weighed, dried overnight at 60°C, and reweighed to establish the rDW.

The blood and tumor samples were prepared for ICP spectroscopy using standard procedures (8). In brief, tumor tissue was digested in 2 ml of concentrated nitric acid overnight in a water heating bath held at 50°C, and blood samples were centrifuged to remove the RBCs from the plasma. Samples were diluted using deionized water, and an ICP optical emission spectrometer (GBC Instruments, Arlington Heights, IL) was used to measure \textsuperscript{23}Na\textsuperscript{+}. The blood sample (at 313.126 nm) concentrations. Assuming that the concentration of \textsuperscript{3}Tm\textsuperscript{3+} in the extracellular space of the tumor is equal to the concentration in plasma, this gives the equation:

\[
\text{rECS} = \frac{[\text{Tm}^{3+}]_{\text{tumor}}}{[\text{Tm}^{3+}]_{\text{plasma}}}
\]

The rECS was calculated using the relation:

\[
\text{rECS} = 1 - \frac{\text{ECS}}{\text{rDW}}
\]

With knowledge of [Na\textsuperscript{+}]\textsubscript{Total} and [Na\textsuperscript{+}]\textsubscript{Plasma}, [Na\textsuperscript{+}] was then calculated as:

\[
[\text{Na}^+] = \frac{[\text{Na}^+]_{\text{Total}} - (\text{rECS} \times [\text{Na}^+]_{\text{Plasma}})}{\text{rICS}}
\]

Similar to the case for rECS, this equation assumes that [Na\textsuperscript{+}]\textsubscript{Plasma} is equal to the extracellular sodium concentration in the tumor. All results are reported as mean ± SE. Data were analyzed by a two-tailed unpaired Student’s t test, and \( P < 0.1 \) was considered statistically significant.

RESULTS

Fig. 2 shows tumor volumes of control and treated animals 2 days before therapy and 1 and 5 days after therapy. Before treatment, control and treated tumors had similar tumor sizes. One day after treatment, there was no significant difference between control and treated tumors (\( P > 0.1 \)). Five days after therapy, however, the tumors treated with 25 mg/kg BCNU were 41 ± 17% smaller than the control tumors (2.4 ± 0.4 cm\(^3\)) versus 4.2 ± 0.6 cm\(^3\), respectively; \( P < 0.05 \). Fig. 2 demonstrates that treated tumors did not display a regression in tumor size but rather a delay in tumor growth. Therefore, the amount of tumor tissue investigated by the surface coil was no different for control and treated tumors. This leads us to conclude that differences in \( ^{23} \text{Na} \) and \( ^{31} \text{P} \) signals were attributable to changes in metabolite concentrations and were not a consequence of simple changes in tumor size or coil filling.

Fig. 3 shows representative SQ (top) and TQF (middle) \( ^{23} \text{Na} \) spectra and \( ^{31} \text{P} \) spectra (bottom) from control (left) and BCNU treated (right) animals 5 days after chemotherapy. The SQ \( ^{23} \text{Na} \) spectra collected with \( t = 6 \text{ ms} \) and \( 45 \text{ s} \), whereas the TQF \( ^{23} \text{Na} \) spectra collected with about three times more acquisitions than the SQ spectrum). It is also interesting to note that the TQF \( ^{23} \text{Na} \) spectra have better signal-noise ratios than the \( ^{31} \text{P} \) spectra, despite the fact that the TQF spectra were obtained in ~45 s, whereas the \( ^{31} \text{P} \) spectra took ~6 min. This is mainly because \( ^{23} \text{Na} \) has very short transverse relaxation time.

The spectra in Fig. 3 demonstrate that control tumors had decreased ATP:P\textsubscript{i} and PCr:P\textsubscript{i} ratios and increased SQ and TQF \( ^{23} \text{Na} \) signal intensities and higher ATP:P\textsubscript{i} and CrP:P\textsubscript{i} ratios. \( ^{31} \text{P} \) resonance assignments: 1) DMMP; 2) phosphonomonesters; 3) P; 4) Cr; 5) γ-ATP; 6) α-ATP; 7) β-ATP.
arising from the reference bulb) at the three time points. Again, there were no significant differences between control and treated tumors 2 days before or 1 day after therapy ($P > 0.1$). Five days after therapy, however, treated tumors had 28% lower SQ $^{23}$Na signal intensity than control tumors (5.3 ± 0.4 versus 7.3 ± 1.1, respectively; $P < 0.1$) and 46% lower TQF $^{23}$Na signal intensity than control tumors (0.49 ± 0.05 versus 0.90 ± 0.17, respectively; $P < 0.05$). It is interesting to note that the differences in SQ $^{23}$Na signal only reached a significance level of $P < 0.1$. The fact that SQ Na$^+$ only reached $P < 0.1$ whereas TQF Na$^+$ reached $P < 0.05$ suggests that the SQ $^{23}$Na signal may not be as sensitive or specific for tumor treatment as the TQF $^{23}$Na signal. Table 1 lists the fast and slow $T_2$ relaxation times of the TQF $^{23}$Na signal from control and treated tumors. There was no significant difference in the relaxation times measured from control and treated tumors at any time point ($P > 0.1$).

Fig. 5 summarizes the $^{31}$P data (ATP:P$_i$ ratio, PCr:P$_i$ ratio, and pH$_i$) collected from control and treated animals at each time point before and after therapy. As in all other measurements, there were no significant differences between control and treated tumors before or 1 day after therapy ($P > 0.1$). Five days after therapy, the ATP:P$_i$ ratio of treated tumors was 126% higher than control tumors (1.8 ± 0.3 versus 0.80 ± 0.24, respectively; $P < 0.05$). At the same time point, treated tumors had 189% higher PCr:P$_i$ ratio than control tumors (1.4 ± 0.3 versus 0.49 ± 0.18, respectively; $P < 0.05$) and 0.17 pH units higher pH$_i$ than control tumors (7.36 ± 0.03 versus 7.19 ± 0.06, respectively; $P < 0.05$). The increased levels of ATP and the more alkaline pH$_i$ found in treated tumors is consistent with a shift from glycolysis to oxidative metabolism, indicating improved cellular energy status as a result of BCNU treatment.

Histological sections of control and treated tumors 5 days after therapy were examined under low-power and high-power magnifications (data not shown). These sections showed clearly that control tumors had large areas of necrosis, whereas treated tumors did not show any large areas of necrosis and contained mostly viable tumor cells. These observations support the findings of the $^{23}$Na and $^{31}$P NMR experiments, which indicated that treated tumors had better cellular bioenergetic status and reduced intracellular Na$^+$ concentration compared with the untreated tumors. The histological findings were consistent with earlier reports (26) showing a ~30% reduction in observations of necrotic cells in tumors treated with BCNU compared with control tumors.

The control and treated animals used in the bench experiments had the similar tumor sizes as the animals used for the NMR experiments (bench experiments: 3.9 ± 0.5 and 2.5 ± 0.3 cm$^3$ for control and treated tumors, respectively; NMR experiments: 4.2 ± 0.6 and 2.4 ± 0.4 cm$^3$ for control and treated tumors, respectively). Table 2 summarizes the tissue compartmentalization of control and treated tumors. The dW and rECS of the treated tumors were identical to those of the control tumors ($P > 0.1$). Naturally, this causes both control and treated tumors to have identical rECS. To validate our measurements, we compared the distribution of TmDOTP$^+$ with CoEDTA$^-$. In both treated and control tumors, we saw identical biodistribution of the two compounds, indicating homogeneous distribution throughout all extracellular spaces.

Fig. 6 demonstrates the total and intracellular sodium concentrations of control and treated tumors. The [Na$^+$]$_{total}$ of treated tumors was 21%...
lower than the control tumors (37.5 ± 1.6 mm versus 47.7 ± 3.5 mm, respectively; P < 0.05). The [Na\textsuperscript{+}] of treated tumors was also 60% lower than the control tumors (9.51 ± 1.17 mm versus 23.9 ± 8.5 mm, respectively; P < 0.05). The relative difference in SQ \textsuperscript{23}Na signal intensity from control and treated tumors 5 days after therapy was statistically identical to the relative difference in [Na\textsuperscript{+}]\textsubscript{total} measured by ICP (28 ± 15% and 21 ± 8%, respectively). This supports the conclusion that SQ \textsuperscript{23}Na NMR spectroscopy can be used to monitor changes in tissue Na\textsuperscript{+}. In a similar fashion, the difference in TQF \textsuperscript{23}Na signal intensity (46 ± 20%) agrees with the difference in intracellular Na\textsuperscript{+} concentration (60 ± 25%), although it should be noted that a large variation exists in both of these measurements. This leads us to conclude that TQF \textsuperscript{23}Na NMR can monitor changes in [Na\textsuperscript{+}]. The TQF signal contains an extracellular component, which may represent as much as 40% of the total signal (11). Although the relative differences in TQF \textsuperscript{23}Na signal intensity and [Na\textsuperscript{+}] are statistically identical, this does not mean that there is no extracellular TQF component. There is a great deal of tumor-to-tumor variation in these measurements (20–30%), and this can mask the effects of an extracellular contribution. In fact, the relative difference in TQF signal intensity is lower than the difference in [Na\textsuperscript{+}], perhaps because of an extracellular component. These experiments show that TQF \textsuperscript{23}Na NMR can be used to monitor changes in [Na\textsuperscript{+}], but they do not define the exact relationship between TQF signal intensity and [Na\textsuperscript{+}].

**DISCUSSION**

We present the first study of SQ and TQF \textsuperscript{23}Na NMR for monitoring response to chemotherapy. Untreated tumor growth was accompanied by decreased ATP:P\textsuperscript{r}, and PCR:P\textsuperscript{r} ratios. These observations have been reported previously in the 9L glioma (25, 26) and other tumors (13–16). Untreated growth also caused increased SQ \textsuperscript{23}Na signal intensity. This is attributable to increased total sodium as a result of increased [Na\textsuperscript{+}]\textsuperscript{total}. TQF \textsuperscript{23}Na signal intensity also increased with untreated growth, most likely because of the increased Na\textsuperscript{+}.

Treatment with BCNU caused tumor growth delay (compared with control tumors), indicating effective tumor cell killing. In agreement with previous reports (24–27), treatment caused an increase in ATP:P\textsuperscript{r}, ratio, indicating improved cellular metabolism in the surviving tumor cells. This improvement in cellular energy status may result from increased perfusion and oxygenation of the tumor, shifting tumor energy metabolism from glycolysis (which only produces two molecules of ATP for each molecule of glucose) to glucose oxidation (which produces 36 molecules of ATP for each molecule of glucose). The decreased SQ \textsuperscript{23}Na signal from treated tumors indicates reduced total sodium. The decreased TQF \textsuperscript{23}Na signal is probably attributable to decreased Na\textsuperscript{+} as a result of improved cellular metabolism.

There have been several earlier reports on \textsuperscript{31}P NMR of 9L gliomas with various doses of BCNU. For example, Steen and Graham (24–27) observed ~100% increase in ATP:P\textsuperscript{r}, and ~300% increase in PCR:P\textsuperscript{r} 4 days after treatment with either 10 mg/kg or 25 mg/kg BCNU. Our study shows similar increases in ATP:P\textsuperscript{r}, but only ~200% increase in PCR:P\textsuperscript{r}. This discrepancy is most likely because of differences in the animal tumor models. All studies involved F344 rats with s.c. 9L tumors, but the tumor sizes and animal weights were vastly different. The previous studies involved rats weighing ~50 g bearing tumors ~8 cm\(^3\) in the control animals and ~3 cm\(^3\) in the treated animals (24–27). This represents tumor body burdens of about 14 and 6% for control and treated rats, respectively. We studied rats weighing ~180 g bearing tumors about 4 or 2.5 cm\(^3\), corresponding to tumor body burdens of about 2 and 1% for control and treated rats, respectively. The larger tumors showed lower PCr:P\textsuperscript{i} ratios and greater changes with treatment in the studies by Steen et al. (24–27) than the smaller tumors in our study.

Steen et al. (25) were also able to see differences in \textsuperscript{31}P metabolite ratios 1 day after treatment before any differences in tumor volume were observed. These results, however, were observed only with higher doses of BCNU (36 mg/kg) and not at lower doses. We chose the lower dose to limit systemic BCNU toxicity in the rats.

The treated tumors showed 0.17 ± 0.6 higher pH\textsubscript{i} compared with untreated control tumors 5 days after therapy. Calculation of pH\textsubscript{i} based upon the chemical shift of the P\textsubscript{i} resonance in \textsuperscript{31}P spectra assumes that very little P\textsubscript{i} is present in the extracellular spaces. In normal tissues, it is well accepted that the vast majority of P\textsubscript{i} arises from the intracellular compartment, but this assumption may not be valid in tumors, especially in the case of therapy. Previous reports have demonstrated that if the rECS does not exceed 55%, the pH measured by \textsuperscript{31}P NMR is largely representative of pH\textsubscript{i} (33). The rECS of the 9L tumors used in this study was determined to be ~21% for both treated and untreated tumors. Therefore, we assume that the pH calculated from the chemical shift of P\textsubscript{i} represents pH\textsubscript{i}. This increase in pH\textsubscript{i} in the treated tumor can result from reduced glycolytic rates and acid production because of improved oxygenation. In addition, the reduced intracellular Na\textsuperscript{+} concentration can increase H\textsuperscript{+} transport out of the cells via the Na\textsuperscript{+}/H\textsuperscript{+} antiporter.

Previous studies have reported dramatic changes in rECS after treatment with BCNU (26). Four days after treatment, histological analysis showed that rECS was five times higher in the treated tumor compared with the control tumor (15.9% versus 3.3%, respectively). Our data, obtained by ICP spectroscopy, shows identical measurements for treated and control tumors. This apparent contradiction can be explained by the fact that the two methods use different definitions of rECS. By histology, rECS is defined as interstitial space, clear of acellular debris, necrotic cells, or cell fragments. By ICP, however, rECS is defined as areas in which the extracellular marker is present. It is clear that histology would count a dramatic increase in necrotic cell population as an increase in rECS. ICP, however, would not detect any difference as long as the necrotic cells were still able to exclude the extracellular space marker. Bhujiwalla et al. (34) measured the rECS of RIF-1 tumors before and after treatment with 5-fluorouracil using \textsuperscript{31}P NMR and radiotabeled markers. In agreement with our results, they found no significant changes in rECS by either method.
We collected a series of TQF $^{23}\text{Na}$ spectra with different preparation times to determine $T_{2p}$, $T_{2g}$, and longitudinal magnetization. This was necessary because changes in $T_{2g}$ or $T_{2p}$ can cause a dramatic change in TQF signal intensity at a particular preparation time, even without any changes in TQ magnetization (7, 11). Therefore, without knowing the relaxation times, changes in TQF signal intensity cannot be attributed to changes in the amount of Na$^+$ undergoing TQ transitions. As shown in Table 1, however, $T_{2p}$ and $T_{2g}$ were statistically identical for control and treated tumors at each time point. This suggests that in these particular experiments, a single TQF spectrum can be collected at one value of preparation time (chosen to maximize signal:noise ratio), and the signal intensity at a particular preparation time, even without any proportional to $T_{2p}$ magnetization. Therefore, TQF $^{23}\text{Na}$ images can be used to quantitatively map TQF magnetization in the tumor during chemotherapy.

Although both $^{23}\text{Na}$ and $^{31}\text{P}$ spectra are consistent with improved cellular metabolism in treated tumors, the $^{23}\text{Na}$ methods may be better suited for monitoring response to therapy. Even TQF $^{23}\text{Na}$ spectra have two to three times higher signal:noise ratio than $^{31}\text{P}$ spectra obtained with optimized parameters for each nuclei. This allows SQ and TQF $^{23}\text{Na}$ images to have better resolutions than is available from $^{31}\text{P}$ CSI. In addition, the single $^{23}\text{Na}$ NMR resonance is much easier to image than the multiple resonances found in $^{31}\text{P}$ spectra. Recent developments in SQ and TQF $^{23}\text{Na}$ MRI of animals (35–37) and in vitro developments in SQ and TQF $^{23}\text{Na}$ MRI of animals (35–37) and $^{23}\text{Na}$ images can be used to monitor responses of tumors to therapy.

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Effects of Chemotherapy by 1,3-Bis(2-chloroethyl)-1-nitrosourea on Single-Quantum- and Triple-Quantum-filtered $^{23}$Na and $^{31}$P Nuclear Magnetic Resonance of the Subcutaneously Implanted 9L Glioma

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