High-Resolution Mapping of Tumor Redox Status by Magnetic Resonance Imaging Using Nitroxides as Redox-Sensitive Contrast Agents


Abstract

Purpose: There is considerable research directed toward the identification and development of functional contrast agents for medical imaging that superimpose tissue biochemical/molecular information with anatomical structures. Nitroxide radicals were identified as in vivo radioprotectors. Being paramagnetic, they can provide image contrast in magnetic resonance imaging (MRI) and electron paramagnetic resonance imaging (EPRI). The present study sought to determine the efficacy of nitroxide radioprotectors as functional image contrast agents.

Experimental Design: Nitroxide radioprotectors, which act as contrast agents, were tested by EPRI and MRI to provide tissue redox status information noninvasively.

Results: Phantom studies showed that the nitroxide, 3-carbamoyl-PROXYL (3CP), undergoes time-dependent reduction to the corresponding diamagnetic hydroxylamine only in the presence of reducing agents. The reduction rates of 3CP obtained by EPRI and MRI were in agreement suggesting the feasibility of using MRI to monitor nitroxide levels in tissues. The levels of 3CP were examined by EPRI and MRI for differences in reduction between muscle and tumor (squamous cell carcinoma) implanted in the hind leg of C3H mice simultaneously. In vivo experiments showed a T1-dependent image intensity enhancement afforded by 3CP which decreased in a time-dependent manner. Reduction of 3CP was found to be the dominant mechanism of contrast loss. The tumor regions exhibited a faster decay rate of the nitroxide compared to muscle (0.097 min⁻¹ versus 0.067 min⁻¹, respectively).

Conclusions: This study shows that MRI can be successfully used to co-register tissue redox status along with anatomic images, thus providing potentially valuable biochemical information from the region of interest.

Magnetic resonance imaging (MRI) provides images with useful spatial and temporal resolutions and aids in the diagnosis of pathologic conditions in soft tissue. In addition to detailed anatomic information from such scans, suitable contrast agents provide important functional information pertaining to blood flow, perfusion, etc. (1). Most contrast agents used for T₁-contrast enhancement contain paramagnetic entities such as the Gd³⁺ complexes and Mn²⁺ complexes. More recently, superparamagnetic iron oxide particles are being used as T₂⁻ contrast agents in MRI especially in cell tracking (2). Nitroxide radicals are organic molecules that have a single unpaired electron and therefore have the potential to provide T₁ contrast similar to gadolinium complexes. Feasibility of nitroxide radicals as T₁ contrast agents in MRI has been examined (3–5) before their use for in vivo EPR imaging as probes (6). However, nitroxide spin probes were reported to be not optimal as MRI contrast agents due to their rapid in vivo reduction to the corresponding diamagnetic products (7). In the living body, paramagnetic nitroxide radicals are chemically and/or enzymatically reduced to the diamagnetic hydroxylamine (8–11). In addition to their biological instability, the relaxivity is lower compared with Gd³⁺-based contrast agents due to the fact that nitroxide probes have only one unpaired electron, as against seven for Gd³⁺. Because of these two characteristics, nitroxide radicals were considered not advantageous as contrast agents for MRI as it was making its entry into diagnostic radiology in the 1980s.

Nitroxide radicals are redox-active species which participate in cellular redox reactions by being oxidized or reduced by cellular redox species. Nitroxides were shown to undergo oxidation to the corresponding oxoammonium cation by superoxide (12, 13) and hypervalent heme species (14). By participating in such redox reactions, they mimic enzymatic actions of superoxide dismutase and catalase. Nitroxides can also be reduced to the corresponding hydroxylamines by...
reductants such as ascorbate, semiquinone radicals, and also by intercepting reducing equivalents from the mitochondrial electron transport chain (10). These features confer to them antioxidant/protective capabilities which may underlie the observed beneficial effects in several pathologic conditions where free radicals are implicated (15). Thus, nitroxides can undergo one-electron oxidation or reduction in the presence of appropriate reactants.

Hypoxic conditions in the tumor microenvironment (16, 17), tissue redox status (18, 19), and oxidative stress accompanying generation of hydroxyl radical (20, 21) and/or superoxide (13, 22) will enhance the conversion of the paramagnetic nitroxide radicals to the corresponding diamagnetic products. In contrast, oxidizing conditions, such as exposure to hydrogen peroxide, could inhibit in vivo reduction of nitroxide radical as well as reoxidize hydroxylamine to the original nitroxide radicals (23). Nitroxide radicals, because of their ability to participate in cellular redox reactions, have been used as spin probes in electron paramagnetic resonance (EPR) imaging to monitor in vivo redox status (6, 17, 24, 25). Therefore, monitoring the rate of transformation of nitroxides to the corresponding diamagnetic species by EPR imaging can provide in vivo assessment of redox status in experimental animals. Such redox mapping based on redox-sensitive paramagnetic spin probes has been carried out by EPR imaging. Although useful information pertaining to cellular redox status was obtained from such studies, often this information could not be associated with specific anatomic regions especially in the heterogeneous environments typical in tumors. In addition, the spatial and temporal resolutions in EPR images are significantly poorer than MRI modalities.

Although nitroxides compare unfavorably to conventional T₁ contrast agents such as Gd³⁺ complexes in terms of relaxivity, being cell permeable, their volume distribution is significantly greater. This can partially compensate for their lower relaxivity being cell permeable, their volume distribution is significantly poorer. In contrast, oxidizing conditions, such as exposure to hydrogen peroxide, could inhibit in vivo reduction of nitroxide radical as well as reoxidize hydroxylamine to the original nitroxide radicals (23). Nitroxide radicals, because of their ability to participate in cellular redox reactions, have been used as spin probes in electron paramagnetic resonance (EPR) imaging to monitor in vivo redox status (6, 17, 24, 25). Therefore, monitoring the rate of transformation of nitroxides to the corresponding diamagnetic species by EPR imaging can provide in vivo assessment of redox status in experimental animals. Such redox mapping based on redox-sensitive paramagnetic spin probes has been carried out by EPR imaging. Although useful information pertaining to cellular redox status was obtained from such studies, often this information could not be associated with specific anatomic regions especially in the heterogeneous environments typical in tumors. In addition, the spatial and temporal resolutions in EPR images are significantly poorer than MRI modalities.

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Materials and Methods

Chemicals. Carbamoyl-PROXYL [3-carbamoyl-2,2,5,5-tetramethylpyrroline-N-oxyl (3CP)] was purchased from Sigma-Aldrich Chem. Co. (St. Louis, MO). Solutions of 4 mmol/L 3CP and 10 mmol/L ascorbic acid were prepared in 50 mmol/L phosphate buffer (pH 7.4) for phantom experiments. For in vivo experiments, 3CP was dissolved in deionized water to obtain a 300 mmol/L (isotonic) solution for i.v. injection to mice.

Animals. Female C3H mice were supplied by the Frederick Cancer Research Center, Animal Production (Frederick, MD). Animals, received at 6 weeks of age, were housed five per cage in climate-controlled, circadian rhythm–adjusted rooms and were allowed food and water ad libitum. Experiments were carried out in compliance with the Guide for the Care and Use of Laboratory Animal Resources (1996), National Research Council, and approved by the National Cancer Institute Animal Care and Use Committee. Experiments were done within 4 weeks of their arrival at the facility. Their measured body weight before the experiments was in the range of 22 to 27 g. A squamous cell carcinoma (SCC VII) tumor was implanted and grown on the right hind leg for a week.

Phantom experiments. A cylindrical phantom (internal diameter, 1.27 cm) was set in the center of a Litz coil resonator (30-mm diameter and 50-mm length) in a 300-MHz EPR or a birdcage-type MRI coil. The cylinder and the connected lines were filled with 50 mmol/L phosphate buffer (pH 7.4). The same volume of 4 mmol/L 1 contrast enhancement per unit volume. For phantom experiments, 3CP was dissolved in deionized water to obtain a 300 mmol/L (isotonic) solution for i.v. injection to mice.

**A** time course of EPR imaging; **B** decay profile in the ROI. C. Time course of % signal change of T₁-weighted spoiled gradient echo MRI; D. The decay profile in the ROI. An identical cylindrical phantom (internal diameter, 1.27 cm) was set in the 30 × 50 mm (diameter × length) Litz resonator operating at 300-MHz EPR or a birdcage-type MRI coil. The cylinder was previously filled with 50 mmol/L phosphate buffer (pH 7.4). Same volume of 4 mmol/L 3CP solution and 10 mmol/L ascorbic acid solutions was simultaneously delivered into the cylinder with same flow rate using a stopped-flow system; then the flow was stopped after the internal volume of the cylinder was completely replaced by the reaction mixture. Scans were started 5 minutes before the starting reaction and repeated by 2.3-minute interval for EPR imaging and 30-second interval for MRI. Time indicated in each image is the time after starting reaction. The image matrix was 128 × 128 for EPR imaging and 256 × 256 for MRI. Field of view was 32 × 32 cm for both experiments. ROI was 11-cm circle, corresponding to 1,597 pixels for EPR imaging and 6,668 pixels for MRI. Semilogarithmic plots of time course of average EPR signal intensity and MRI signal change in the ROI were shown below the corresponding images (B and D). Decay rate constants were obtained from the slope of linear portion of the decay curves.

![Fig. 1. A comparison of EPR imaging and T₁-weighted spoiled gradient echo MRI by a phantom experiment.](Image)
3CP solution and 10 mmol/L ascorbic acid solutions was simultaneously delivered into the cylinder with the same flow rate using a stopped-flow mimicking system, and the flow was stopped after the internal volume of the cylinder was completely replaced by the reaction mixture. Scans were started 5 minutes before starting the reaction and repeated at 2.3-minute intervals for EPR imaging and at 30-second intervals for MRI.

**Total nitroxide volume in tissues.** A 300 mmol/L 3CP solution (isotonic) was injected at a dose of 1.5 μmol/g b.w. in the tail vein of squamous cell carcinoma tumor-bearing mice under isoflurane (1.5%) anesthesia. The normal femoral muscle and tumor tissues were collected as a function of time (5, 7.5, 10, 15, and 20 minutes). Then, these samples were diluted in 4-fold volume of PBS, homogenized, and mixed with ferricyanide solution (2 mmol/L in final), which quantitatively converts the hydroxylamine produced as a result of in vivo reduction back to the nitroxide radical form. The sample (100 μL) was measured by X-band EPR and the concentration of nitroxyl contrast agent was determined from standard curve of nitroxyl contrast agent dissolved in PBS, which included ferricyanide (2 mmol/L). The operating conditions of X-band EPR spectrometer were as follows: microwave frequency, 9.4 GHz; microwave power, 1 mW; modulation frequency, 100 kHz; modulation width, 1 Gauss; sweep rate, 25 Gauss/min; and time constant, 0.064 s.

**In vivo two-dimensional EPR imaging experiments.** Mice were anesthetized by isoflurane (1.5%) in medical air (700 mL/min). The mouse was placed in a special lucite mouse holder with adhesive tape and put in the Litz coil resonator (30-mm diameter and 50-mm length; ref. 27). The tail vein was cannulated for the injection of 3CP. The core temperature of the mouse was maintained at –37°C using an air heater. Data acquisition was started immediately after injecting 3CP.

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**Fig. 2.** EPR-based redox imaging. 
A, geometry of mouse and the resonator and the view of two-dimensional EPR image. The mouse was set in the 30 × 50 mm (diameter × length) Litz resonator tuned to 300 MHz. The two-dimensional (x-z) EPR imaging gives a transmission image, in which all information along y-axis was overlapped on a single x-z matrix. 
B, two-dimensional EPR images of mouse legs obtained repeatedly after injection of 3CP. The image matrix was 128 × 128. Field of view was 6 × 6 cm. The insertion is a display of image at 6.4 minutes (maximum intensity) with half dynamic range, which was used to select ROIs. A contour line of the mouse legs was predicted on this image, and then ROI-1 for normal leg and ROI-2 for tumor-bearing leg were estimated. 
C, time course of average intensity in the ROI-1 and ROI-2. Semilogarithmic values of averaged image intensity in the ROIs were plotted with time. Decay rate constants were obtained from the slope of linear decay after peak. 
D, decay rate map showed a distribution of decay rates calculated pixel-wise. Almost no anatomic information was obtained on the EPR-based decay rate mapping.
The linear portion of the decay curves. Both EPR imaging and MRI showed similar reduction rates of image intensity, which in turn reflects nitroxide levels. This result shows that, using the T1 contrast capability of nitroxides, it is possible to monitor time-dependent changes in image intensity. The good agreement of the reduction rates of image intensity between EPR imaging and MRI suggests that MRI may have advantages over EPR imaging with respect to both spatial and temporal resolutions in following the time-dependent changes in nitroxide levels.

A schematic drawing of the geometry of the mouse and the resonator is shown in Fig. 2A. Figure 2A shows the schematic arrangement of the two legs of the mouse in the resonator with orientation with the magnetic field and the view of two-dimensional EPR image. Figure 2B shows a time course of two-dimensional spatial images of nitroxide probes obtained by CW EPR imaging after an i.v. injection of 3CP. The image in Fig. 2B (bottom row, extreme right) is a display of maximum intensity image (6.4 minutes) with 33% dynamic range, which was used to select ROIs. A contour of the mouse legs was chosen on this image, and then ROI-1 for normal leg and ROI-2 for tumor-bearing leg were selected. The image intensities of both legs were found to decrease with time. However, information related to anatomic structures of mouse legs could not be obtained by EPR imaging. The blur in the EPR image is due to broad line width of the nitroxide (1.2 Gauss) compared with the scan width (10 Gauss). Line width deconvolution was not applied because the deconvolution technique may introduce artifacts in intensity for reliable quantification. The semilogarithmic values of the averaged image intensities in the ROIs were plotted as a function of time after injection of the probe (Fig. 2C). Over the time course, image intensity increased to a maximum value and subsequently decreased with time in both the normal leg and tumor-bearing leg. A decay rate was obtained from the linear part after maximal image intensity was achieved using the least squares method and summarized in the Table 1. It was also found that the normal leg intensity in the normal leg (650 ± 99, n = 3) was significantly smaller than that in the tumor-bearing leg (1,175 ± 168, n = 3) when the values were analyzed by paired t-test with two-tailed comparison (P < 0.05). The pixel-based reduction rates of the nitroxide 3CP were computed and the corresponding image displayed in Fig. 2D.

Figure 3A shows the schematic arrangement of the tumor-bearing mouse in the resonator and the slices selected for MRI experiments. An axial slice including the center part of tumor was selected from the scout images. A total of 60 spoiled gradient echo images were obtained during the 20 minutes scan. Therefore, one image was obtained every 20 seconds. The

<p>| Table 1. Decay constant of nitroxide radical by means of EPR spectroscopy, EPR imaging, and MRI |
|-----------------------------------------------|-----------------------------------------------|
| Normal leg                                    | Tumor leg                                     |
| Decay rate (min⁻¹)                            | Decay rate (min⁻¹)                            |</p>
<table>
<thead>
<tr>
<th>n</th>
<th>Decay rate (min⁻¹)</th>
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<th>Decay rate (min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPR imaging</td>
<td>0.0783 ± 0.0230</td>
<td>3</td>
<td>0.0870 ± 0.0233*</td>
</tr>
<tr>
<td>MRI</td>
<td>0.0069 ± 0.0108</td>
<td>3</td>
<td>0.0973 ± 0.0090*</td>
</tr>
</tbody>
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NOTE: Values are indicated as mean ± SD. n, number of experiments. *P < 0.05, between the normal leg and the tumor leg (paired t-test with two-tailed comparison).
initial six images (obtained before injection) were averaged. Then, each subsequent image was divided by the averaged baseline image, multiplied by 100, and finally subtracted by 100 to obtain percent difference ($D\%$).

$$D\%_{i,m,n} = \frac{S_{i,m,n}}{\sum_{i=1}^{n} (S_{i,m,n})/6} \times 100 - 100 \quad (1)$$

where $i$ is number of data set, $m$ and $n$ is image matrix, and $S$ is pixel intensity. Spoiled gradient echo–based $T_1$-weighted images showed increasing intensity after administration of 3CP (Fig. 3B). The image (bottom row, extreme right) in Fig. 3B shows the $T_2$ map of the same slice calculated from previously obtained multislice multiecho images. The regions of interest ROI-1 and ROI-2 were chosen based on the $T_2$ map for normal and tumor legs, respectively. The spoiled gradient echo image intensity exhibited an immediate increase by nearly 30%, after which a gradual decrease was noted. Figure 3C shows semilogarithmic plots of the averaged percent difference in the ROI-1 and ROI-2. The normal tissue exhibited a slight delay to reach maximum intensity. The image obtained 0.5 minute after injection showed signal increase only in tumor tissue. However, the image obtained 1.8 minutes after injection showed similar signal level in both the tumor and normal tissues. Maximum enhancements in the tumor ($28.7 \pm 6.9$, $n = 3$) and normal ($27.3 \pm 8.5$, $n = 3$) tissues were of similar level. Decay constants in the ROIs were obtained by the least squares method and

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**Fig. 3.** MR-based redox imaging. A, geometry of mouse and the resonator and the view of MRI. Mouse legs were placed on the center of a bird-cage type resonator designed for mouse worked on 200 MHz. B, time course of % signal change of $T_1$-weighted spoiled gradient echo MRI and a scout $T_2$ mapping for ROI selection. ROI-1 for normal leg and ROI-2 for tumor leg were estimated based on a previously obtained $T_2$ mapping. The image matrix was $256 \times 256$. Field of view was $3.2 \times 3.2$ cm. C, time course of average % signal change in the ROI-1 and ROI-2. Logarithmic values of % signal change in the ROIs are plotted with time. Decay rate constants were obtained from the slope of linear decay after peak. D, decay rate map overlapped on the corresponding multislice multiecho image can show a distribution of decay rates with clear anatomic information.
summarized in Table 1. From these results, it can be seen that the decay rate in the tumor leg was significantly faster than the normal leg, in agreement with the results obtained from EPR imaging experiments. The pixel-wise reduction rates of nitroxide 3CP were computed and overlaid on a scout multislice multiecho image (Fig. 3D). The MR-based redox mapping shows clear difference of decay rates of 3CP between tumor and neighboring normal tissues.

Figure 4 showed a time course of total (nitroxyl radical + hydroxylamine) amount of 3CP in the normal and the tumor tissues after the i.v. injection. The total amounts of 3CP in both tissues were almost stable during the time period (5-20 minutes) used in both imaging experiments although a rapid reduction of the nitroxide 3CP to the corresponding hydroxylamine was observed (29). The average amount of 3CP of five time points was 1.55 ± 0.086 μmol/g tissue in the tumor tissue and 1.37 ± 0.068 μmol/g tissue in the normal muscle. No significance was obtained between average amounts in the tumor and normal tissues when the values were analyzed by paired t test with two-tailed comparison.

Discussion

For the past several years, nitroxides have been exclusively used in EPR imaging redox imaging; however, the results of the present study now expand their application as functional redox-sensitive contrast agents for MRI. The significant enhancement in image intensity induced by 3CP administration and the superior temporal and spatial resolution of MRI modality suggest that it is advantageous to monitor the pharmacokinetic distribution of nitroxides using T1-weighted MRI compared with EPR imaging. The major advantages of using nitroxides in MRI as opposed to EPR imaging include the availability of MRI scanners (both for human and small animal studies), multislice imaging capability, enhanced spatial and temporal resolution, and coregistration of images of tissue redox status with anatomic information inherently available from MRI.

Results shown in Fig. 4 suggest that the decreasing intensity of EPR imaging and MRI was due to the reduction of nitroxyl radical rather than clearance. Nitroxides, having a single unpaired electron, can undergo redox transformations between the one-electron oxidized state, the oxoammonium cation, and the one-electron reduced hydroxylamine (Fig. 5). The oxoammonium/nitroxide redox pair constitutes an effective redox couple and supports catalytic activities such as superoxide dismutase mimetic activity and catalase activity (13, 14), which may underlie its protective effects in cells and tissues subject to oxidative damage (15). Although the nitroxide/hydroxylamine pair is not capable of supporting these catalytic processes, it is actively involved in protective activities by scavenging reactive oxygen species. Nitroxide free radicals also participate in radical-radical recombination reactions avidly and thus can neutralize reactive oxygen species (21). The hydroxylamines, on the other hand, can function as conventional H-atom donors such as ascorbate and scavenger free radicals by H-atom transfer (30). The oxoammonium cation can be reduced by one- or two-electron steps to the corresponding nitroxide or hydroxylamine, respectively (12–14). Nitroxides provide protection in cells and tissues against diverse types of insult, such as exposure to superoxide and hydrogen peroxide, by directly scavenging the ROS (31). In addition to protection by radical scavenging, nitroxides also evoke cellular responses such as cell signaling–specific pathways (32, 33). The ability to trigger cell signaling–specific pathways has been postulated to support possible antitumor effects of nitroxides in vivo (34, 35). When nitroxides are incubated with cells or administered in vivo, a dynamic equilibrium is established between the nitroxides and hydroxylamines (29, 36, 37). The equilibrium levels of these species are dependent on tissue oxygenation and the levels of reducing equivalents or the tissue “redox status” (18, 38).

The therapeutic effects of nitroxides have been evaluated in animal models against diverse types of damage or in spontaneously developing pathologic conditions. Nitroxides were found to be effective protectors in various disease models involving free radicals in experimental animals (39). Based on their efficacy as protectors in these studies, they were recently tested in humans (40). Topical application of the nitroxide Tempol was found to be effective in limiting radiation-induced...
alopecia in human scalp, an adverse effect in radiotherapy with free radical involvement. The efficacy of these agents has been attributed to their radical scavenging efficiency and, being low molecular weight compounds, their ability to accumulate at effective concentrations in critical subcellular compartments. Based on these and other ongoing studies, nitroxides may be potential candidates for systemic administration in humans for therapeutic purposes in various pathologic conditions. Therefore, there exists a need to monitor their levels in vivo with currently available clinical imaging modalities.

MRI studies on phantom objects containing the nitroxide 3CP show that it is possible to elicit sufficient $T_1$ contrast enhancement despite their lower relaxivity $[-0.2 \text{ (mmol/L)}^{-1}\text{s}^{-1}]$ compared with Gd$^{3+}$ complexes $[4 \text{ (mmol/L)}^{-1}\text{s}^{-1}]$. One advantage of the lower relaxivity of nitroxides in MRI is that a linear response between the concentration and intensity enhancement can be expected. It is then possible to quantify by making rapid $T_1$ assessments. In vivo MRI experiments using 3CP at doses well tolerated in mice also show that it is possible to monitor their accumulation and clearance in the tissues/organs of interest. Recently, the in vivo distribution of spin-trapped nitric oxide using the Fe(II)-chelated N-methyl-d-glucamine dithiocarbamate as a spin-trap agent was obtained by $T_1$-weighted spin-echo MR imaging at 1.5 T (41).

The biological instability of nitroxide free radicals, which was a major limitation as a $T_1$ contrast agent in providing sufficient image intensity enhancement in earlier studies, can now be exploited to report on tissue redox status. This will be possible provided that the clearance of the agent and its metabolite is not the major contributor to the observed time-dependent decrease in image intensity resulting from $T_1$ contrast. Ex vivo analyses of nitroxides and hydroxylamines after in vivo administration of 3CP in tumor-bearing mice show that within the time window, the levels of (nitroxide + hydroxylamine) are practically invariant whereas the nitroxide levels decrease (29, 36, 37). Thus, the change in the image intensity in MRI as a function of time can be attributed predominantly to nitroxide reduction. The nitroxide reduction rates, which depend on tissue redox status, were found to be higher in tumor compared with muscle by both EPR imaging and MRI. As first noted by Swartz et al. (25) and Berliner et al. (6), nitroxides have the capability to serve as hypoxia-sensitive contrast agents whereas hydroxylamines can serve as oxygen-sensitive pro-contrast agents (42). Monitoring profiles of reduction/oxidation of nitroxide/hydroxylamines in normoxic/hypoxic tissue may actually serve as a viable approach to assess the global redox status in tissue using EPR imaging or MRI. The pharmacokinetics of nitroxide spin probe can be obtained using either EPR imaging or MRI. Although EPR imaging can detect nitroxide free radicals itself directly and obtain images of nitroxide free radical distribution as well as redox maps, the poor image resolution and lack of anatomic detail limit its use in the clinical setting presently. On the other hand, the $T_1$-weighted MRI serves as an indirect detection modality of nitroxide contrast agents. The $T_1$-weighted spoiled gradient echo–based dynamic MRI can give appropriate tumor redox status information with useful anatomic resolution. Such capabilities may be clinically useful when nitroxides are used as radio-protectors of surrounding normal tissue while delivering therapeutic doses of radiation to tumors. MRI studies with nitroxides could be potentially used to optimize treatment schedules based on the maximal possible difference of nitroxide levels in normal and tumor regions.

References
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