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Original Research Article

Usefulness of clinical magnetic resonance scanners for imaging experimental changes in laboratory rodents' central nervous system

Dorota Mystkowska[a,*], *Anna Tutas*[a], *Katarzyna Jezierska-Woźniak*[a], *Anita Mikołajczyk*[a], *Barbara Bobek-Billewicz*[b], *Marek Jurkowski*[b]

[a]*Department of Neurology and Neurosurgery, Faculty of Medical Sciences, University of Warmia and Mazury in Olsztyn, Poland*
[b]*Department of Nuclear Medicine and Endocrine Oncology, The Maria Skłodowska-Curie Memorial Cancer Center, Institute of Oncology, Gliwice Branch, Poland*

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ABSTRACT

Introduction: Magnetic resonance imaging (MRI) is a noninvasive technique applied in medical diagnosis and for studying animal models of human diseases. MRI offers longitudinal *in vivo* studies without the need to sacrifice animals, thus making data easier to compare. The number of required animals can be limited.

Aim: The aim of this article was to present the potential role of clinical MRI scanners in the management of central nervous system visualization and injury in rodents on the basis of the current literature.

Materials and methods: Clinical small bore scanners with field strength from 0.1 T to 3 T are used for imaging the nervous system of rodents *in vivo*.

Results and discussion: The employment of clinical scanners equipped with dedicated human coils, for small objects imaging, results in the reduction of image quality. It is caused by a small signal-to-noise ratio (SNR). The way to increase the SNR is to use clinical scanners for imaging particular parts of the human body, e.g. head, or dedicated coils for imaging small parts of the human body, e.g., thumb or wrist, or to use dedicated small animal coils to image multiple animals in the larger bore of the clinical scanner at the same time. For some neurobiological experiments clinical scanners seem to be sufficient. Although clinical MRI scanners are widespread, not many laboratories use them for small animal research.

Conclusions: Clinical scanners with surface coils dedicated to small human organs, or with dedicated small animal coils, are useful for imaging experimental changes in the central nervous system of laboratory rodents.

*Correspondence to: Stem Cells Laboratory, Faculty of Medical Sciences, University of Warmia and Mazury, Warszawska 30, 10-082 Olsztyn, Poland. Tel.: +4889 524 53 38; fax: +4889 524 53 18.
E-mail address: dorota.mystkowska@uwm.edu.pl (D. Mystkowska).

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1. Introduction

Magnetic resonance imaging (MRI) is a method based on magnetization of hydrogen atomic nuclei which begin to rotate in the magnetic field. Hydrogen nuclei are excited with a radio frequency, caused by a special transmitting coil. The signal generated by rotating nuclei is detected by the receiving coil, and processed by special computer systems. This method was used for the first time for clinical research at the beginning of the 1970s. Presently, it is widely applied for imaging entire body structures.

The application of MRI into diagnostic procedures was a breakthrough in the assessment of central nervous system (CNS) structures.[22] MRI allows for evaluating anatomical conditions before elective surgeries. In the case of brain tumors, it allows for localizing the tumor and its malignancy. MRI makes it possible to asses radicality of resection, shows post surgical lesions and the differentiation or recurrence of the neoplastic process.[1,12] Advanced MRI techniques allow for the analysis of tumor or necrotic tissue properties, and provide more accurate information on its nature.[2] MRI is the only method that allows a direct visualization of the spinal cord, and with the help of a high contrast resolution it facilitates detecting early stage lesions. This method allows one to assess the totality of vertebrae and intraspinal structures, as well as damage in paraspinal soft tissues.[16]

In medical diagnosis, MRI scanners with field strengths of up to 3 T are used. The quality of obtained images is enhanced by an increase in magnetic field strength. It enables the imaging of smaller structures.

MRI provides an opportunity to monitor lesions *in vivo* in experimental therapies, with the use of animal models, such as rats and mice, in order to transpose results for the planning of clinical examinations. This method contributes to reducing both costs and the number of animals needed.

Using clinical MRI scanners is connected with the problem of small object volume. It is important to increase the signal-to-noise ratio (SNR). The way to increase the SNR is to use small clinical (for imaging thumb or wrist) or dedicated animal coils, or clinical scanners designed for imaging parts of the body, e.g., head scanners.[6] To enhance the signal, contrast agents with magnetic properties are applied. Furthermore, a larger bore of the clinical scanner offers the possibility to image multiple animals at the same time, when using a larger standard coil (e.g., human head coil, birdcage coil).[3,6]

2. Aim

The aim of this paper is to present the role of clinical MRI in the management of the CNS anatomy and injury in rodents on the basis of the current literature.

3. Materials and methods

Clinical small bore scanners with field strength from 0.1 T to 3 T are used for imaging the nervous system of rodents *in vivo*.

4. Results

4.1. *Scanners with a magnetic field strength of 0.1 T*

A low magnetic field strength (0.1 T) Bouhnik SAS scanner (Vélizy-Villacoublay, France) is the weakest reported scanner. The experiment was conducted on 4 male Wistar rats, weighing 250–400 g. Rats were anesthetized with isoflurane (1.5–2.0% pushed by air). Cerebral tumor growth was induced by injecting the C6 glioma cell line. Two weeks after the cells implantation, the imaging was carried out. T1-weighted images demonstrated a deviation of brain ventricles to the left, due to the development of the tumor. T2-weighted images visualized the inflammatory reaction and necrosis in the brain's right hemisphere.[4] The authors estimated the tumor size to be 505 mm^3.

4.2. *Scanners with a magnetic field strength of 1.5 T*

There are many reports concerning the use of clinical MRI scanners with the field strength of 1.5 T for the purpose of small animal imaging.[5,11,13,14,15,17,18,19,20] A clinical Magnetom Symphony scanner (Siemens Medical Solutions, Erlangen, Germany) with standard, commercially available coils (Head Array Coil, Double Loop Array Coil, Loop Flex Coil, Siemens Medical Solutions, Erlangen, Germany) was used in the experiments performed on male RH-RNU and Wistar rats, weighing 250–300 g. RH-RNU rats were anesthetized with an intraperitoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg) in sterile saline. The Wistar rats were anesthetized with chloralhydrate (300 mg/kg) injected intraperitoneally. Rat model of bacterial meningitis was used to prove the usefulness of a clinical MRI scanner for small animal imaging. The imaging was performed before and after the administration of the contrast agent Magnevist (0.3 mmol/kg) into the femoral vein, with T1- and T2-weighted images. The authors demonstrated that the resolution achieved in clinical MRI scanners is sufficient for imaging small animals, and allows one to visualize pathological lesions. Imaging parameters are presented in Table 1.[14]

A clinical MRI scanner operating at the field strength of 1.5 T was used to monitor tumor growth in female nude mice as well.[6] In this experiment clinical scanners: Magnetom Symphony, Sonata or Avanto (Siemens, Erlangen, Germany) with standard small loop RF-coil (Siemens, Erlangen, Germany) were used for imaging purposes. Mice were anesthetized with an intraperitoneal administration of ketamine (100 mg/kg) and xylazine (5 mg/kg). Tumor growth was induced by the injection of the U-87 MG glioma cells into the right caudate nucleus. One week after the cells implantation, groups of 5 animals were exposed to radiotherapy with different doses of radiation: 5×1 Gy, 5×2 Gy and 5×3 Gy, with 24 h intervals. Three weeks after the tumor cells injection, MRI was performed on the control group (without radiotherapy) and on all 3 groups treated with radiation therapy, before and after the administration of the contrast agent Magnevist (0.4 mL intraperitoneally). This experiment finally managed to establish a correlation between the dose of radiotherapy and tumor size. Tumor growth was apparently suppressed in mice that were treated with higher

Table 1 – Account of acquisition parameters depending on the main magnetic field strength of the clinical MRI scanners.

Examined structure	Magnetic field strength	Race of animal	Sequence	TR/TE (ms)	Flip angle (deg.)	Matrix size (pixels)	Pixel size (μm)	Slice thickness/ gap (mm)	Voxel size (mm^3)	Field of view	Number of excitations	Number of slices acquired
Brain	1.5 T, Thorsen et al.[19]	Rat – BD-IX	T1-weighted SE	440/14	NS	256 × 256	200 × 200	2.0/0	0.080	50 mm	NS	13
			T2-weighted TSE	4000/96		256 × 256						19
	1.5 T, Brockmann et al.[6]	Mouse – Nude mouse	T1-weighted	400/15	NS	NS	160 × 160	1.0/0	0.026	52 mm 134 mm	NS	NS
			T2-weighted	2500/53								
	1.5 T, Linn et al.[14]	Rat – Wistar, RH-RNU	T1-weighted	462/20	NS	384 × 384	160 × 160	1.3/0.1	0.033	60 mm	10	12
			T2-weighted	3800/75				1.5/0.1	0.038	60 mm	5	
	1.5 T, Ulmer et al.[20]	Rat – Wistar	T1-weighted	550/16	NS	128 × 128	NS	2.0/0	NS	64 mm	NS	NS
			T2-weighted	3171/120								
			T2-weighted DCE	30/14		64 × 64		1.5/0		90 mm		15
	2 T, Jurkowski and Bobek-Billewicz[11]	Rat – Wistar	T1-weighted	500/22	NS	256 × 256	NS	1.0/0	NS	NS	NS	NS
			T1-weighted									
			T2-weighted	4000/126		256 × 254						
			T2-weighted	3900/126		256 × 254						
	2.35 T, Brekke et al.[3]	Rat – Nude rats (Han: MU/RNU Rowett Nude)	T2-weighted RARE	6000/60	NS	128 × 128	NS	1.0/1.2	NS	3 cm	4	11
			T2-weighted FLAIR	2500/60		128 × 128		1.0/1.2			2	11
			T1-weighted SE	2000/8.8		64 × 64		3.0/3.5			NS	3
			T1-weighted SE	1500/8.8								
			T1-weighted SE	500/8.8								
			T1-weighted SE	300/8.8								
			T1-weighted SE	100/8.8								
			T1-weighted SE DCE	407/13		256 × 256		1.0/1.2		3 cm	4	11
	3 T, Jurkowski and Bobek-Billewicz[11]	Rat – Wistar	T1-weighted	652/23	NS	100 × 336	NS	1.0/0	NS	NS	NS	NS
			T1-weighted	633/23		140 × 180						
			T1-weighted	2500/100		140 × 480						
			T2-weighted			100 × 336						
			T2-weighted									
			T2-weighted FLAIR	6000/284		100 × 224		1.0/0.5				
	3 T, Chang et al.[7]	Rat – Spraque–Dawley	T2-weighted	3000/100	150	256 × 192	NS	2.0/0.1	NS	7 cm	2	NS
			T2-weighted	231/10	25							
	3 T, Engelhorn et al.[8]	Rat – Fisher	T1-weighted	507/17	NS	512 × 512	NS	1.0	NS	40 mm	NS	4–5
			T2-weighted	2800/96				NS		40 mm		
	3 T, Yamamoto et al.[21]	Rat – Wistar, Spraque-Dawley	T1-weighted FSE	1500/14	NS	256 × 256	NS	1.5/0.5	NS	40 × 30 mm^2	10	NS
			T2-weighted FSE	4100/128							8	
			SPGR	53/5.5	45	NS	156 × 156	0.2/0	0.005	8 × 6 cm	1	
			T2-weighted EPI	142/22.1	20	64 × 64	625 × 625	3.0/0	1.172	40 × 40 mm	NS	
Spinal cord	1.5 T, Stoll et al.[17]	Rat – Lewis	T1-weighted	460/14	NS	NS	NS	3.0/0	NS	NS	NS	NS
			T2-weighted	2500/80								
	1.5 T, Stoll et al.[18]	Rat – Lewis	T1-weighted	460/14	NS	NS	NS	3.0/0	NS	NS	NS	NS
	1.5 T, Levene et al.[13]	Mouse – C57B1/6	T2-weighted FSE	4000/85	NS	512 × 512	NS	0.9/0	NS	60 mm	4	NS

Comments: NS – not specified.

doses of radiation (5 × 3 Gy) compared to the other groups. MRI scans were compared with histological specimens, which confirmed the results received with MRI and allowed to calculate the tumor size. Imaging parameters are presented in Table 1.

A clinical Vision scanner (Siemens, Erlangen, Germany) with small loop coil (Siemens, Erlangen, Germany) was used for imaging rat gliomas.[19] During these experiments male and female BD-IX rats, weighing 50–100 g, were used. Tumor growth was induced by the injection of the BT_4C tumor cell line into the brain 2.5 mm below the cortical surface. Six weeks after the injection imaging was performed before and after the administration of the contrast agent Omniscan (1 mL of 0.5 mmol/mL). On T1-weighted images without the contrast agent, only the border of the tumor was visualized; however on T1-weighted images with contrast, entire tumors were, easily identified. T2-weighted images showed peritumoral edema. MRI results were compared with histological specimens. Tumor volume of the T1-weighted images with contrast predicted well the real size of the lesion as proven by histology. In the remaining MR images, tumors were larger than those observed in histological specimens. Imaging parameters are presented in Table 1.

A similar experiment was performed with a clinical Achieva scanner (1.5 T, Philips, the Netherlands) and standard surface coils (small surface receive-only coil, Microscopy coil 47, Philips, Best, the Netherlands) to monitor glioma in rats.[20] Brain tumor was induced by the injection of the C6 glioma cell line. The experiment was conducted on 10 male Wistar rats, weighing 200–250 g. Animals were anesthetized with an intraperitoneal administration of 4% chloralhydrate (1 mL/100 g). The contrast agent Magnevist (0.3 mL) was injected into the femoral vein. Tumor size on T1-weighted images with the contrast agent correlated with the volume observed histologically. T2-weighted images indicated peritumoral edema. Imaging parameters are presented in Table 1.

Levene et al.[13] carried out the imaging of mice spinal cord by an MR-Signa Excite Imager scanner (GE Medical Systems, Milwaukee, WI, USA) and wrist coil. For their experiment, they used 2 female C57Bl/6 mice, weighing 15–20 g, with an induced spinal cord injury. Animals were anesthetized with 0.1 mL pentobarbital injected intraperitoneally. Within the injured area of the spine, a higher signal intensity was observed. The lesion area was significantly distinguishable from intact regions. Similar observations were accomplished on histological specimens carried out after MRI examinations. Imaging parameters are presented in Table 1.

Using a Magnetom Vision scanner (Siemens, Erlangen, Germany) and Small Loop Flex coil (Siemens, Erlangen, Germany) proved to be effective to visualize the nerves of the cauda equina and the sciatic nerve in Lewis rats.[14,16] Animals were anesthetized with an intraperitoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg). Imaging scans were performed before and after the administration of contrast agents: Gadofluorine M – 0.1 mmol/kg, Magnevist – 0.2 mmol/kg[14,17] and Super-paramagnetic Iron Oxide Particles (SPIO) – 0.2 mmol/kg.[14,16] Imaging parameters are presented in Table 1.

4.3. *Scanners with a magnetic field strength of 2 T*

Jurkowski and Bobek-Billewicz[11] used a clinical MRI scanner with a magnetic field strength of 2 T (Elscint, Philips, the Netherlands) and orbital surface coil, for the purposes of rat brain imaging and monitoring and managing experimental brain tumors. Wistar rats were used. Animals were anesthetized with an intramuscular injection of vetbutal in a dosage of 100 μL/100 g. Tumor growth was induced by the injection of the C6 glioma cell line. The macroscopic view on the 20th day after the implantation is presented in Fig. 1.

MR imaging was performed 20 days after tumor cell injection before and after the injection of the contrast agent Gadovist. T1-weighted contrast-enhanced images are presented in Fig. 2.

Following MRI, histological tests of the specimens were performed, and they confirmed lesions showed by MRI scans (Fig. 3).

Imaging parameters are presented in Table 1.

4.4. *Scanners with a magnetic field strength of 2.35 T*

A clinical MR scanner (Bruker Biospec Advance DBX-100 horizontal bore magnet, Bruker, Ettlingen, Germany) with a magnetic field strength of 2.35 T and saddle-shaped RF coil, was used to visualize glioma in rats.[3] Experiments were performed on 19 nude rats with immunodeficiency. Animals

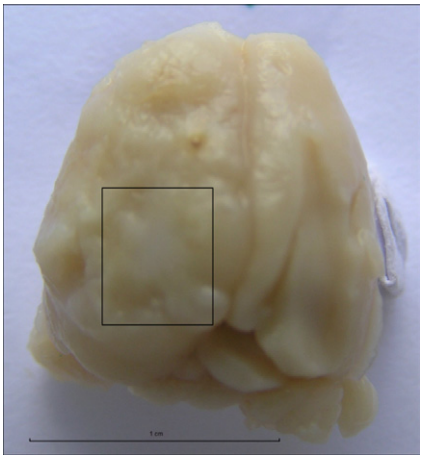

Fig. 1 – Macroscopic view of rat brain tumor on the 20th day after cancer cells implantation. The black rectangle indicates tumor.

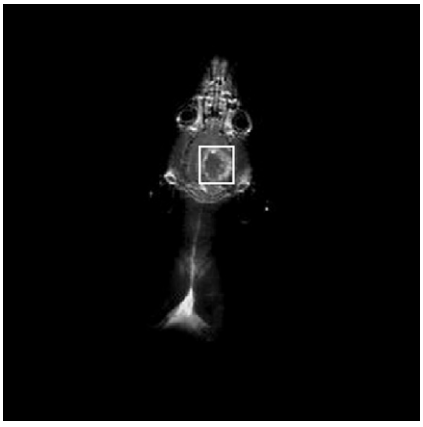

Fig. 2 – T1-weighted image of rat brain tumor with contrast agent, 20 days after cancer cells implantation, coronal plane. The white rectangle indicates tumor.

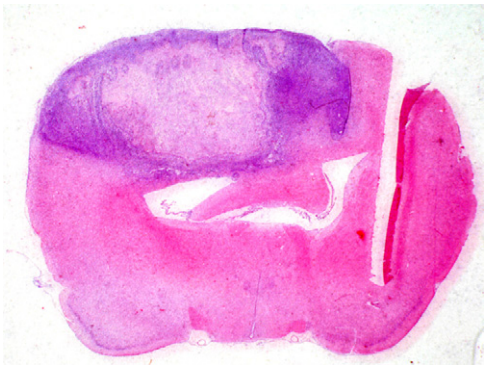

Fig. 3 – Histological image of rat brain tumor 20 days after cancer cells implantation, transversal section.

weighted about 30 g. Both rat sexes were used to exclude hormonal effects on tumor growth. Tumor growth was induced by the injection of a human glioblastoma cell line (U251N), transfected with a transmembrane proteoglycan NG2. NG2 expression in tumor cells causes an aggressive disease course. It increases tumor cell proliferation in vitro and promotes angiogenesis *in vivo*.[3] For the purpose of MR imaging, rats were anesthetized with the inhalation of 1–2% isoflurane in a mixture of volume ratio 30% O_2 and 70% N_2. Imaging was carried out before and after the administration of the contrast agent Gadomer in a dosage of 0.2 mmol/kg to check vascular permeability and blood volume. Moreover, the contrast agent Omniscan in a dosage of 0.5 mmol/kg was used to monitor microvascular parameters. This experiment demonstrated a significantly greater tumor growth in rats with an active NG2 gene, compared to the control group with an absence of the NG2 gene. It was caused by a higher number of vessels. Histological specimens from rats with an NG2 expression showed a dense vasculature, large, dilated thin-walled vessels with tightly packed erythrocytes. Tumors in the control group had a more homogeneous structure with small, tightly packed tumor cells and capillary vessels. Imaging parameters are presented in Table 1.

4.5. *Scanners with a magnetic field strength of 3 T*

As often as 1.5 T, scanners with a magnetic field of 3 T were used.[7,8,11,21] Yamamoto et al.[21] imaged a rat brain by a Signa scanner (GE, Healthcare, Milwaukee, WI, USA) and dedicated animal solenoid coil with a diameter of 42 mm. For their experiments they used 3 male rats, weighing 400–600 g. Animals were anesthetized with an intramuscular injection of ketamine (33 mg/kg) and xylazine (6.6 mg/kg). The first rat, Sprague–Dowley was used for imaging the entire brain. T1- and T2-weighted images allowed researchers to show the location of small anatomical structures, such as caudate putamen, striatum, corpus callosum, and hippocampus. The second rat, also Sprague–Dowley was used for imaging brain blood vessels. Researchers succeeded in visualizing internal carotid artery (ICA), azygos anterior cerebral artery (AZACA), and middle cerebral artery (MCA). The structures of the cortical branches of MCA were different between the right and left hemispheres. The third rat, Wistar, was used for contrast-enhanced imaging. The contrast agent Magnevist (0.1 mmol/kg) was injected into the tail vein. Imaging after contrast administration facilitated the detection of arterial input function (AIF) in the MCA region. AIF served to measure cerebral blood flow, cerebral blood volume and mean transit time.[10,21] Imaging parameters are presented in Table 1.

A clinical MRI Magnetom Tim Trio scanner (Siemens Medical Solutions, Erlangen, Germany) and wrist coil to detect stem cells in the CNS were used by Chang et al.[7] In 10 Sprague–Dawley rats, weighing 250–300 g, an intracerebral hemorrhage was triggered. One week later, SPIO-labeled neural stem cells (NSCs) were injected into the left striatum. Clinical MRI allowed the researchers to show the migration of stem cells in the hemorrhage area. After the imaging, 2 rats were sacrificed and their brains were submitted for histopathological and immunohistochemical analyses, which confirmed the presence of NSCs in the area showed by MRI scans. Imaging parameters are presented in Table 1.

A clinical Tim Trio scanner (Siemens, Erlangen, Germany) and orbital surface coil with a diameter of 40 mm were used to visualize glioma in rats.[8] In this study, 14 female Fisher rats, weighing 150–200 g, were injected with the F98 tumor cell line. Ten days after the implantation, MR imaging was performed. Animals were anesthetized with an intraperitoneal injection of ketamine (70 mg/kg) and xylazine (15 mg/kg) mixture. Each animal received a double dosage of the contrast agent Magnevist (0.2 mmol/kg) intravenously. The authors obtained images of acceptable quality, which allowed them to calculate tumor volume. Also micro-CT, and histological examinations were performed. MRI- and CT-derived tumor volumes were compared to histology results. There was a positive correlation between these tumor volumes, without significant differences. Imaging parameters are presented in Table 1.

Jurkowski and Bobek-Billewicz[11] performed a visualization of the medication carrier with the use of a clinical Achieva scanner (3 T, Philips, the Netherlands) and wrist coil. They implanted a biodegradable foil disk with a diameter of 800 μm and a thickness of 100 μm, moistened with cytostatics (doxorubicine and idarubicine) to a Wistar rat's brain. The position of the implanted disk is presented in Fig. 4.

Animals were anesthetized with the administration of vetbutal in a dosage of 100 μL/100 g. MR imaging was performed 10, 20 and 30 days after the implantation in axial, coronal and sagittal planes, on T1- and T2-weighted images, before and after a subcutaneous injection of 1 mL of the

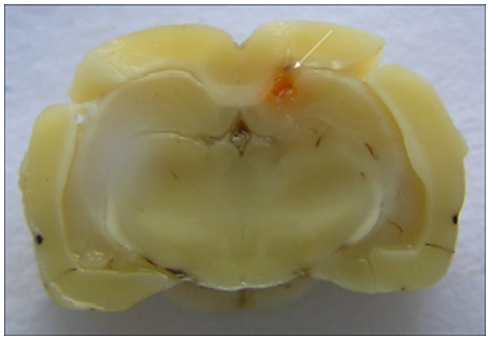

Fig. 4 – Macroscopic view of rat brain, transversal plane. The white arrow indicates the point of the disk with doxorubicin implantation.

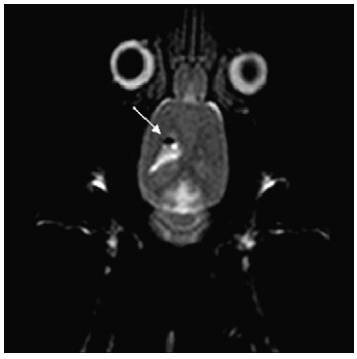

Fig. 5 – T2-weighted image of rat brain on the 20th day after disk implantation with doxorubicin, coronal plane. The white arrow indicates the point of disk implantation.

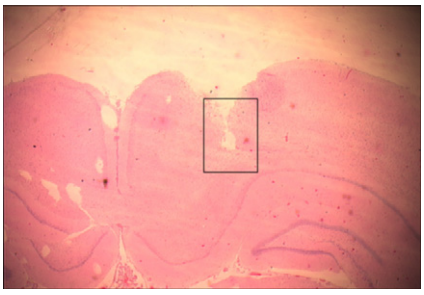

Fig. 6 – Histological localization of the area visible in MR images on the 20th day after the implantation of the disk with doxorubicin. The black rectangle indicates the point of disk implantation.

contrast agent Gadovist. T2-weighted image on the 20th day after disk implantation is showed in Fig. 5.

MR images were compared to histological specimens, and disk degradation was checked (Fig. 6).

Imaging parameters are presented in Table 1.

5. Discussion

Research involving small animals provides very important information concerning pathogenesis and tumor growth, and may help to determine how to cure CNS diseases in humans. The use of clinical scanners with clinical coils for small animal imaging is possible. A satisfactory resolution can be obtained to visualize structures of interest to researchers and pathological lesions induced experimentally.[9] Furthermore, a larger bore of the clinical scanner offers the possibility of imaging multiple animals at the same time, when using a larger standard coil, e.g., human head coil.[11] The widespread usage of clinical scanners potentially contributes to the more common use of MRI scanners in experimental research.[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22]

6. Conclusions

Clinical scanners with surface coils dedicated to small human organs, or with dedicated small animal coils, are useful for imaging experimental changes in the CNS of laboratory rodents.

Conflict of interest

None declared.

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