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MR imaging-guided cryoablation of metastatic brain tumours: initial experience in six patients

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Abstract *Objective:* The objective was to evaluate the initial experience and safety of magnetic resonance imaging (MRI)-guided transcranial cryoablation in cystic metastatic brain tumours. *Material and methods:* Seven cystic metastatic brain tumours in six patients were treated with cryoablation. The approval from the local ethics committee and individual patient consent were acquired before the study. Before the procedure the tumours were detected with conventional CT or MRI. The procedure was performed under local anaesthesia and conscious sedation. A 0.23-T open MRI system with optical tracking was used for procedural planning, instrument guidance and procedural monitoring of the ice ball formation. An MR-compatible, argon-based cryoablation system was used. The schedule of follow-up imaging ranged from 12 days to 12 months. *Results:* Seven treatment sessions were performed. All the cryoprobes were successfully inserted into the target with one pass. All the patients tolerated the procedure well without experiencing any neurological deficits during the treatment phase or during the immediate post-treatment period. One patient died 12 days after cryoablation. *Conclusion:* MR-guided and monitored metastasis brain tumour cryoablation is technically feasible and may represent an alternative treatment in selected patients.

Keywords Interventional MR · Metastasis · Brain · Cryoablation

Introduction

Brain metastasis is the most common brain malignancy in the adult population and constitutes a continuous challenge in oncology. Although recent advances in surgery, radiosurgery and chemotherapy have broadened treatment options, there still is no consensus treatment for these patients [1]. Surgical resection is the gold standard but this always carries the disadvantage of causing damage to healthy brain tissue, especially if a long access path is required to reach deeply located lesions. The disadvantage of radiotherapy is lack of repeatability because of cumulative dose effects [2]. The benefits of the use of systemic chemotherapy can be limited by the inability of most chemotherapeutic agents to penetrate the blood–brain barrier, thus reducing the response rate of brain metastases to systemic chemotherapy. There still is no statistically significant improvement in survival demonstrated with any of the treatments described above, as a stand alone or combination therapy [1]. Furthermore, there is a subgroup of patients with chemoresistant or radioresistant metastases with a dismal operative prognosis. Therefore, there is a moral obligation to investigate new, effective, minimally invasive therapy options that preserve neurological function and improve the quality of life.

Intracranial real-time magnetic resonance imaging (MRI)-guided laser thermal therapy for focal metastatic brain tumours has been advocated as being both feasible and safe [3]. Cryoablation is an effective tumour ablation method that has distinct benefits not shared by the other thermal ablation methods [4–8]. Based on this information, it can be hypothesised that transcranial

cryoablation is likely to be equally as effective as laser ablation in the treatment of metastatic brain tumours. The purpose of this study was to evaluate initial experience with MRI-guided cryoablation in metastatic brain tumour treatment.

Materials and methods

Interventional MR imaging system

A 0.23-T open configuration MRI system with integrated optical frameless tracking for stereotaxy (Panorama, Philips Medical Systems, Finland) was used for all procedural guidance and monitoring. The interventional MRI system consisted of an MRI system, in-room monitor, in-room MRI user interface, infrared camera, MRI fixed infrared mirrors and a foot pedal for operator-controlled imaging [9]. The MRI unit is an open biplanar C-arm resistive magnet, and the tracking system consists of a handheld instrument mounted tracker linked to an infrared camera array via reflecting spheres. The stereotaxy is provided by four light-reflecting spheres located at the ends of the handheld instrument mount and four at the upper pole of the magnet, respectively. The user interface supports probe-guided imaging and provides a fixed reference frame. The subject is fixed to the table. The imaging planes included those perpendicular to and in the plane of the probe. During the procedure, the instrument trajectory and its relationship to the target were displayed as a real-time graphic overlay in acquired image sets. The details of the optical tracking system have been previously reported [10].

Cryoablation system

Cryoablation was performed with an MR- and biocompatible, argon-based cryoablation system (CryoHit; Galil Medical Ltd, Israel). This system consisted of a computer workstation, a gas gauge, a gas distribution system and accessories, e.g. needle-like cryoprobes, temperature sensors and a remote control device [8]. Heat exchange occurs along a 2-cm-long segment at the distal end of each cryoprobe.

Patient selection and preparation

The study protocol was approved by the local human subjects committee and informed consent was obtained from all patients before the procedure. Only patients with cystic metastatic brain tumours were included in the study. The patients received a detailed narrative of conventional surgical and noninvasive therapy options after which cryoablation was performed at their own request. Patients with normal haemostasis values, no history of active ischaemic heart disease, Karnofsky performance status [KPS] score greater than 70, and no contraindications to MR imaging were regarded as eligible for treatment. Seven brain tumours in six consecutive patients (five women, one man, mean age 53 years) were treated with 11 cryoablation procedures. One patient with two tumours underwent two sessions. The second session took place 1 week after the first. Lesion sizes, locations and diagnoses are demonstrated in Table 1. The maximum tumour size was limited to 4.0 cm.

Procedural infection prophylaxis was achieved by intravenous administration of antibiotic (1.0 g of cefazolin sodium). Mannitol (250 ml) and ethamsylate (2.0 g) were administered by intravenous drip to reduce intracranial pressure and as a precaution against haemorrhage during the procedure. All patients underwent the procedure under conscious sedation using diazepam (5 mg) administered intravenously (i.v.). Local anaesthesia was administered with subcutaneous and local injection of lidocaine (2%, 5 ml). MRI contrast agent (gadolinium-DTPA, 0.2 ml/kg) was administered intravenously to achieve better MRI visualisation of the lesion and the surrounding anatomy, especially the vessels.

Table 1 MR imaging-guided brain metastases cryoablation: patient, tumour and therapy characteristics

No.	Age/sex	Tumour characteristics			Cryotherapy		
		Location	Size (cm)	Primary tumour	Probe (mm)	Maximum ice ball size	Probe positions
1	F/51	Left basal ganglia area	4.1×3.1	Lung cancer	2	2.3×2.0	2
2	F/56	Left parietal lobe	2.2×2.3	Lung cancer	2	2.0×1.6	1
3	F/52	Left temporal lobe	3.8×3.7	Breast cancer	2	2.4×2.0	2
4	F/53	Left temporal lobe	3.6×3.2	Breast cancer	2	2.3×2.0	2
5	M/52	Left temporal lobe	2.8×2.6	Lung cancer	1.47	2.0×1.6	1
		Left cerebellum	2.4×2.1		1.47		1
6	F/54	Left temporal lobe	3.0×3.2	Lung cancer	1.47	2.0×1.7	2

F female, *M* male

Procedure

The patient was positioned arbitrarily in the appropriate position with respect to both the required image quality and the access to the tumour. The head was fixed to the table with adjustable straps. Imaging and therapy were performed on a movable table that could be rolled in and out of the device. A flexible transmit–receive-type surface coil (diameter 20 cm) was used for procedural imaging. During the procedure, the operator communicated with the patients, ordering extremity motion intermittently to ensure that the cortical functions remained intact.

Completely balanced steady state (true-FISP) (CBASS 3D 8 slice, TR 8.4 ms, TE 4.2 ms, flip angle 45°, slice thickness/slice interval 5.0 mm/5.0 mm, FOV 300×300, matrix 180×216, acquisition time 45 s) images were obtained in transverse, sagittal and coronal planes preoperatively and the target was selected accordingly. The site of the skin puncture and the procedural route were defined from the stereotactic image provided by optical tracking. Once the intervention route was planned, the scalp was opened under local anaesthesia and a drill hole was made through the skull bone by a radiologist and a neurosurgeon. This was done outside the MRI field's 5-gauss line because the bone trephine was not MRI compatible. A 3-mm burr hole was made in the skull at the entry point. Once the dura had been exposed and penetrated, the patient was moved into the MRI device. At this time, the coaxial needle entry to the lesion site was initialised. Continuous multiplanar field echo T1WI (FE 5 slice, TR 125 ms, TE 7.0 ms, flip angle 60°, slice thickness/slice interval 7.0 mm/7.0 mm, FOV 300×300, matrix 160×180, acquisition time 25 s) and CBASS 3D images were used to plan the passage so as to avoid critical brain regions and important vascular structures as the MR-compatible (14-gauge, 15-cm length) neuroneedle or 14G neurocut (Invivo Germany GmbH, Germany) advanced through the brain.

Once the needle tip had reached target, tumour cyst aspiration was performed immediately before the cryoablation with the aspiration material being collected for histopathological and cytological evaluation. Subsequently the cryoprobe was inserted through the coaxial needle into the tumour. The coaxial needle was then retracted 2 cm in order to expose the active area of the probe. The cryoablation was performed using two freeze-thaw cryoablation cycles (10-min freeze, 5-min thaw, 10-min interval). In cases where the tumour was too large to be entirely covered by one ice ball, the cryoprobe was withdrawn 2.0 cm or the angle of the insertion changed until the freezing zone covered the tumour volume entirely (Fig. 1). One patient with two tumours underwent two sessions with the second tumour being treated with cryoablation 7 days later. During the cryoablation, the ice ball size was monitored using MR imaging. CBASS imaging was repeated at 1-min intervals in two perpendicular planes to monitor the change in the ice ball size and the treatment progress. The number of cryoneedles needed in the procedure was determined according to the size, shape and location of the tumour. At the conclusion of the procedure, MRI was performed to reveal any associated complications and to visualise the immediate therapeutic effect with the following parameters: T1WI (fast spin echo (FSE), 5 slices, TR 125 ms, TE 7.0 ms, flip angle 60°, slice thickness/slice interval 7.0 mm/7.0 mm, field of view 300×300, matrix 160×180, acquisition time 28 s) and T2WI (5 slice, TR 430 ms TE 16 ms, flip angle 90°, slice thickness/slice interval 7.0 mm/7.0 mm, field of view 300×300, matrix 160×192, acquisition time 28 s).

After the procedure, patients received an intravenous drip of mannitol (125 ml/day), intravenous drip of

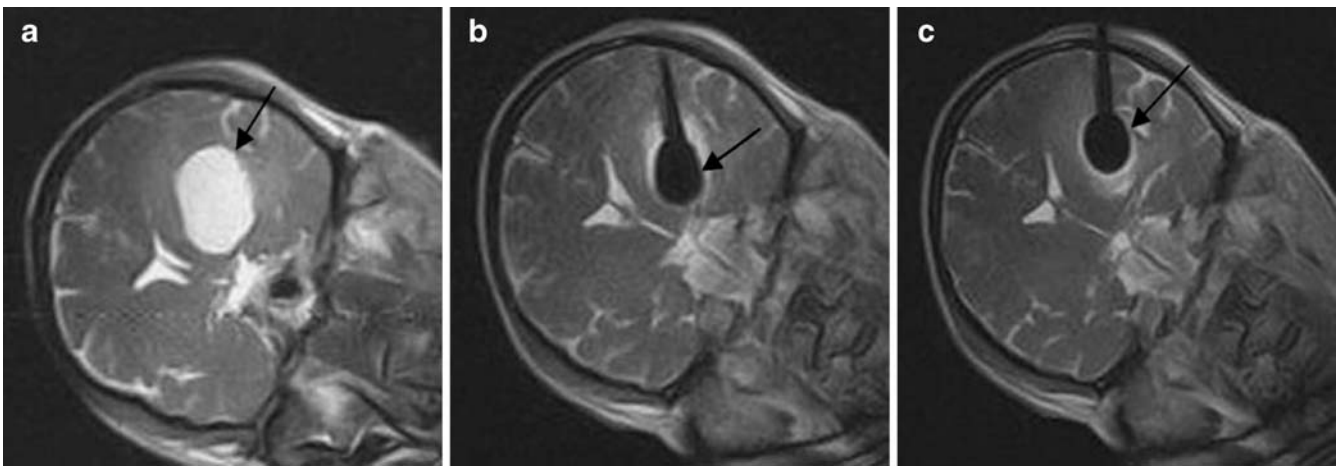

Fig. 1 MR-guided cryotherapy in a 51-year-old woman with basal ganglia area metastasis from lung cancer. **a** Coronal 0.23-T image obtained before the procedure shows a high signal intensity cystic tumour (*arrow*). **b** Coronal 0.23-T image obtained during the procedure shows ice ball formation at the distal part of the tumour (*arrow*). **c** Coronal 0.23-T image shows the probe withdrawn 2 cm and the ice ball developing at the proximal part of the tumour (*arrow*) in order to achieve complete ablation

corticosteroid (dexamethasone, 10 mg/day), and antibiotic (cefazolin sodium, 1 g/day i.v.) during the hospitalization period in order to control intracranial pressure and for infection prophylaxis. The hospitalisation times ranged from 3 to 14 days (mean 6.8 days) and the follow-up periods varied from 12 days to 12 months

Results

All cryoablation procedures were successful. The lowest measured temperature at the tip of the cryoprobe was −185°C. The size of lesion decreased with the hydatid fluid aspiration. The mean operation time from penetrating the skull to the end of the procedure was 120 min. During the freezing, the ice around the probe tip was continuously visible as an ellipsoid-like signal-free area in the MR images.

All patients tolerated the procedure without exhibiting any neurological defects during the treatment phase or during the immediate postoperative period. Follow-up information is shown in Table 2. One patient died as a result of a secondary complication 12 days after the cryoablation. Two patients experienced transient symptoms possibly related to intracranial hypertension, such as increased body temperature (<38.5°C), headache and nausea lasting 24 h after the procedure. Five patients survived more than 3 months.

On follow-up MRI conducted 3 and 7 days after the procedure, the lesions showed the typical appearance of cryocoagulation necrosis. On follow-up MRI performed 6 weeks from the procedure the lesions had further decreased in size (Fig. 2).

Discussion

There are studies showing that MR-guided heat-induced ablation can be relatively safely and effectively applied to brain tumours located at surgically inaccessible sites [2, 11–15]. In contrast to hyperthermia-based ablation methods such as those based on laser or radiofrequency, cryoablation possesses specific beneficial properties [5]. Cryoablation requires no specific temperature-sensitive pulse sequences to visualise the progress of therapy with MRI. In addition, the freeze-induced necrotic region can be exactly defined in the brain [16]. While the hyperthermia-induced lesion size may increase within the first 10 days because of delayed heat effects [17], cryoablation zone volume does not expand after the cryoablation procedure [18], meaning that cryolesion size is very predictable. This is a very important feature in brain tumour treatment because the cranial cavity volume is limited and any increase in ablation zone volume can cause intracranial hypertension and tissue displacement leading to possible cerebral oedema.

Generally, our experience with this initial, limited series suggests that MR imaging-guided percutaneous cryotherapy of brain metastases is applicable in selected patient groups. In all, six tumours were treated completely in a single session. The mean operative time of 120 min was not excessively prolonged for conscious patients to tolerate.

There are several factors that potentially affected the procedural safety in our series. A previous animal study has shown lesion increases in related oedema, most pronounced at 3 days after cryotherapy after which they gradually declined until the14th postoperative day, when the oedema had disappeared [18]. One contributing factor may be the aspiration that was applied to brain tissue bearing up to two cystic metastases, with fluid aspiration preceding the cryoablation, which reduced the tumour volume, possibly decreasing the side effects caused by cryoablation-related oedema. The thin needle-like cryoprobes avoid excessive damage to the neural structures along the puncture route helping to preserve normal tissue and neurological function, a feature that is especially important in treating lesions in confined spaces such as the cerebellar region. Intravenous MRI contrast agent was administered to achieve better visualisation of the lesion in relation to the surrounding critical structures, such as sigmoid sinus. These two procedural elements may contribute to safer treatment of tumours without any cystic component.

We had a procedure-related complication. One patient died after the cryoablation. From the 3rd postoperative day the patient became gradually disoriented and diseased on

Table 2 Complications, follow-up, residual, relapse and survival from the patient data

No.	Complications	Follow-up imaging	Residual at treatment site	Relapse	Survival
1	Fever, pneumonia, death	At 12 days	None	None	12 days
2	None	Not available	Not available	Not available	Alive at 3 months
3	None	At 12 months	None	At 12 months	Alive at 12 months
4	Fever, headache,	At 3 days and 1.5 months	None	None	Alive at 3 months
5	Fever, headache, nausea	At 7 days	None	None	Alive at 3 months
6	None	Not available	Not available	Not available	Alive at 3 months

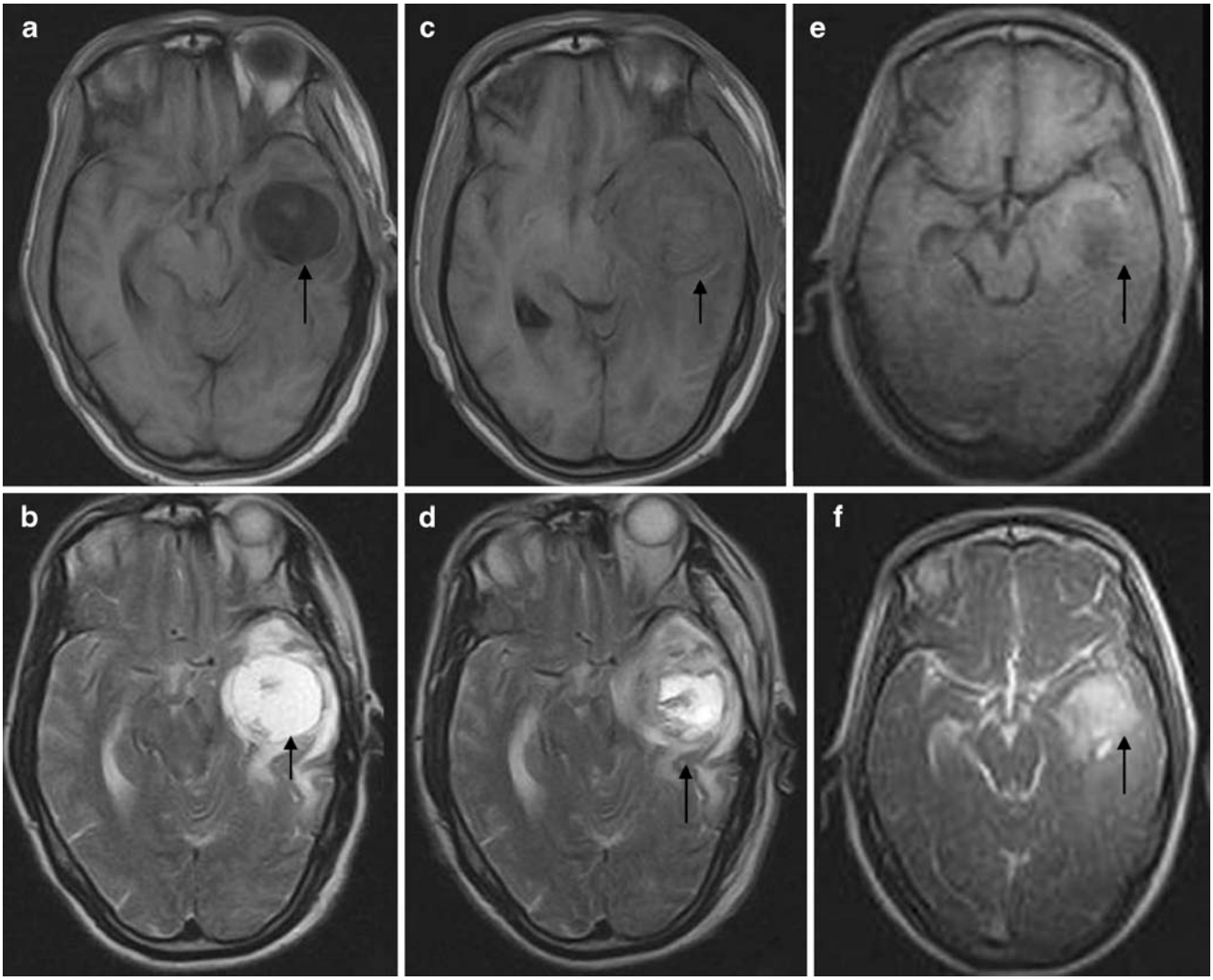

Fig. 2 Cryotherapy in a 52-year-old woman with temporal lobe metastasis from breast cancer. **a**,**b** Preprocedural images: transverse 1.5-T FSE-T2WI images show the tumour located in the left parietal lobe as a hypointense lesion on T1WI (*arrow*) and a hyperintense lesion on T2WI (*arrow*). **c**,**d** Three days later after cryoablation: transverse 1.5-T FSE-T2WI and FSE-T1WI images show the tumour appearing as an isointense lesion on T1WI (*arrow*) and a heterogeneous lesion on T2WI (*arrow*). **e**,**f** One and a half months later after cryoablation: transverse 0.23-T FSE T1WI and transverse FSE T2WI images show that the cryoablated tumour has decreased in size

the 12th postoperative day. It is possible that the symptoms were related to the treatment although there were no immediate signs of complications after the procedure. Regarding the one fatality in our series utmost consideration in patient selection is needed. Deep situated tumours should be considered for treatment only when chemoresistant or radioresistant metastases need immediate treatment to avoid terminal disease progression and the patient would not be expected to endure more invasive procedures.

There are several obvious limitations to our study. The sample size was small and the study group was selective, hence the obtained results do not necessarily reflect the treatment effect that would be expected with a larger patient group. Also, our study did not include any patients at a high risk of therapy-related intracranial pressure increase from treating large solid metastases. It is possible that this particular subset of patients would have exhibited a different treatment response than the patients described in this study. In addition, we had poor follow-up, which significantly reduces the value of the study. The reason for the lack of imaging follow-up was that many patients declined any further medical care, imaging included. Finally, the low-field strength MRI system can be considered a drawback, because functional brain imaging and spectroscopy are not possible, potentially compromising patients' functional capabilities. In our series, where

none of the tumours could be considered to lie near to important cortical functional zones according to the preoperational imaging, and the patients were conscious during the whole procedure, the absence of fMRI can be tolerated.

We conclude that MRI-guided and monitored intracranial tumour therapy with cryoablation is technically feasible in selected patients. It seems that intracranial cryoablation may offer an alternative treatment method and does not preclude other treatment options.

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