

Gadovosfiset Trisodium (Vasovist®) Enhanced MR Lymph Node Detection: Initial Observations

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Abstract: The aims of this study were to identify: (i) whether intravenous administered Vasovist® is taken up by lymph nodes, (ii) the time of peak enhancement and (iii) the optimal MR sequence. Ten rectal cancer patients were evaluated with 4D THRIVE MRI at 0, 15, 30 and 60 minutes and with 3D T1W GRE at 0, 7, 17 and 32 minutes after intravenous Vasovist® administration. The signal intensity (SI) of individual lymph nodes, muscle, mesorectal fat and iliac artery on all images were measured with regions of interest and were evaluated. At histopathological examination 56 nodes were eligible for analysis. The results showed that (i) intravenously administered Vasovist® shows enhancement in normal lymph nodes in rectal cancer patients, (ii) peak of enhancement is 15 (4D THRIVE) and 17 (3D T1W GRE) minutes and (iii) the 3D T1W GRE is the most optimal MR sequence.

INTRODUCTION

Accumulating evidence favours a tailor-made neoadjuvant approach for rectal cancer patients to further reduce the highly variable local recurrence rate [1]. To select this optimal treatment accurate preoperative prediction of the most important risk factors is crucial. One of these factors is the nodal status and therefore accurate preoperative prediction of the nodal status is necessary for the selection of the most optimal treatment strategy. However, prediction of the nodal status remains a problem for the radiologist. The results of a meta-analysis show that Endoluminal Ultrasound (EUS), Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) all lack clinical accuracy for identification of nodal disease [2]. This can be explained by the fact that all modalities primarily use size criteria to distinguish malignant from benign mesorectal nodes and size criteria are proven to be unreliable in rectal cancer patients, because of the high rate of small (<5 mm) malignant nodes in rectal cancer patients [3,4].

A great deal of research is being done to solve this inaccurate nodal status prediction. Will *et al.* showed in a meta-analysis that nodal status prediction is feasible with Ultrasound Superparamagnetic Iron Oxide (USPIO) MRI [5].

A recent study of Herborn *et al.* established that interstitial MR lymphography with depiction of direct tumor invasion in the nodes was feasible using Vasovist® contrast agent in rabbits [6]. Vasovist® is an intravascular gadolinium based

contrast agent and was originally designed for blood pool MR imaging. If Vasovist® is feasible to detect nodal metastases in rectal cancer patients, than it would be a promising alternative to USPIO as a lymph node specific MR contrast agent. Vasovist® is administered through an intravenous bolus during the MRI examination which is less cumbersome to patients and the diagnostic team as compared to the administration of USPIO. The latter needs an infusion of 45 minutes, 24-36 hrs before MR scanning, requiring a double visit for one MR scan.

The aims of this pilot study were therefore (i) to identify whether intravenous administered Vasovist® is taken up by lymph nodes in rectal cancer patients, (ii) to assess the time of peak enhancement after i.v. administration of Vasovist® and (iii) to assess the optimal MR sequence to depict these enhanced mesorectal lymph nodes in rectal cancer patients.

MATERIALS AND METHODS

Patients

During the study period between June 2006 and August 2006 a total of ten patients (7 males, 3 females, mean age 71, range 32-86 years) were diagnosed with biopsy proven primary rectal cancer at our hospital. All rectal tumors were defined by an inferior tumor margin not farther than 15 cm from the anal verge as described by endoscopy. Every patient was required to give full written consent and the protocol was approved by the institutional review board.

Vasovist® Contrast Agent

Vasovist® (Gadovosfiset Trisodium, Bayer Schering Pharma, Berlin, Germany) is an intravascular contrast agent designed specifically for blood pool imaging, or MR angiography. This contrast agent is a formulation of a stable gadolinium diethylenetriaminepentaacetic acid (GdDTPA)

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chelate substituted with a diphenylcyclohexylphosphate group (gadofosveset trisodium), and binds reversible to the human protein albumin. Vasovist® injection is a clear, colourless to pale yellow liquid. The dose used was 0.12 ml/kg body weight (equivalent to 0.03 mmol/kg). An MR-compatible power injector (Spectris; Medrad, Indianola, Pa) was used to administer Vasovist® as a single intravenous bolus injection at 1.5 ml/s followed by a 25 ml normal saline flush.

MR Imaging

MR imaging was performed on a 1.5T system Gyroscan, Powertrak 6000, NT release 6.2.1, 23•0 mT.m, rise time 0•2 ms, slew-rate 105 T 1/ms (Philips Medical Systems, Best, Netherlands) using a pelvic phased array coil with the patient in feet-first, supine position. Sequences used are sagittal and axial 2D T2 weighted TSE. 4D THRIVE images were obtained with 3.3/1.23 (TR/TE), 10 degree flip angle, a 384 x 384 matrix, and 1 mm slice thickness using keyhole imaging. T1-weighted images were obtained with 10/4.60 (TR/TE), 15 degree flip angle, a 384 x 512 matrix, and 1 mm slice thickness to locate lymph nodes and to differentiate them from blood vessels. Table 1 shows more details concerning the MR protocols of both sequences. All axial images were angled perpendicular to the tumor. Patients did not receive bowel or other preparation. The total scan duration was around 70 minutes.

Table 1. The MR Protocols for the 4D THRIVE and 3D T1W GRE Sequences

	4D THRIVE	3D T1 GRE
TR	10	3.3
TE	4.60	1.23
Matrix size	384 x 384	512 x 512
Thickness	1 mm	1 mm
Gap	0	0
Fat saturation	SPIR	None
Plane	Axial	Axial
# Slices	160	200
Turbofactor	50	1
Time	2:01 min	6:31 min

Image Evaluation

An MR radiologist (3000 pelvic MR reading experience) evaluated all MR images prospectively and blinded for the histological results and recorded the exact localization of each visible lymph node depicted by 3D T1-weighted GRE MR images by means of an anatomical map. This was used as a template to help detecting the nodes on the other sequences at different time intervals.

The signal intensity (SI) of the total node (SI_{TN}), gluteus muscle (SI_{muscle}), mesorectal fat (SI_{fat}) and that of the left iliac artery (SI_{artery}) were measured by placing regions of

interest (ROI's). This was done before Vasovist® injection on the axial 4D THRIVE sequence and was repeated 15, 30 and 60 minutes after Vasovist® injection. This imaging examination was also performed on axial T1 GRE images before and at 7, 17 and 32 minutes after Vasovist® administration. These signal intensities were used to calculate the following ratios:

SI_{TN}/SI_{muscle} , SI_{TN}/SI_{fat} and SI_{TN}/SI_{artery} for the 4D THRIVE and 3D T1W GRE sequence at the different time intervals. If the ratio before ($t = 0$) is compared to the ratio after administration of Vasovist®, then this can be used as an indicator for Vasovist® enhancement within the lymph nodes. The Vasovist® enhancement is based on the blood pool characteristics in combination with the well perfused normal lymph nodes. This Vasovist® enhancement causes a rise in signal intensity within a benign lymph node compared to the signal intensity of the node before Vasovist® administration. This implies that a high ratio of SI_{TN}/SI_{muscle} or SI_{TN}/SI_{fat} is associated with a high enhancement of Vasovist®. The SI_{TN}/SI_{artery} will show the concentration of Vasovist® within the node in comparison to the Vasovist® in the vessels at different time intervals.

Histopathological Evaluation

The standard surgical procedure was a Total Mesorectal Excision, as described by Heald [7], performed within two weeks after the USPIO MRI. The rectum with the complete surrounding mesorectal fat and mesorectal lymph nodes was removed by sharp dissection along the mesorectal fascia. The histological examination was standardized: the specimen was fixed in formalin for 24-48h and after that the circumferential resection plane was inked. The specimen was then sectioned transversely every 5 mm and thus also perpendicular to the mesorectum. A careful search for lymph nodes was made in each histological tissue slice by a dedicated pathologist. Harvested lymph nodes were placed in trays, and processed according to standard methods and stained with haematoxylin-eosin. The pathologist, blinded to the radiological findings, reported the nodal status.

Statistical Analyses

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS®, version 12.0.1, Inc., Chicago, IL). The results of all ratio calculations are given as the mean ± standard deviation (SD). The Wilcoxon signed-rank test was used to compare the results of the ratio calculations before and after Vasovist® administration.

RESULTS

At histopathological examination three of the ten patients had a positive nodal status. Of the 76 lymph nodes found on MR images, 20 nodes were too small (<2 mm) for the ROI's to be accurately positioned. Of the 56 nodes eligible for analysis, 41 nodes were distributed among the seven patients with a N0 status. Of these 41 nodes, 39 nodes showed a peak increase in signal intensity. This means that only 2 (5%) nodes, both in one patient, in this group did not show Vasovist® enhancement. Of the remaining 15 nodes distributed among the three patients with a positive nodal status, 6 (40%) nodes did not show Vasovist® enhancement. All 8 (2+6) nodes with no signal increase were distributed among

four patients. Three out of these four patients were confirmed to have a positive nodal status at histopathological examination (Fig. 1).

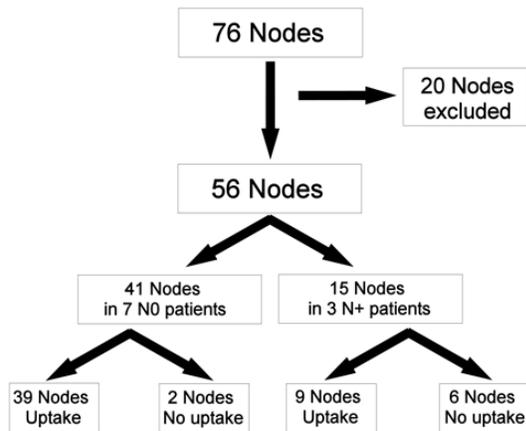
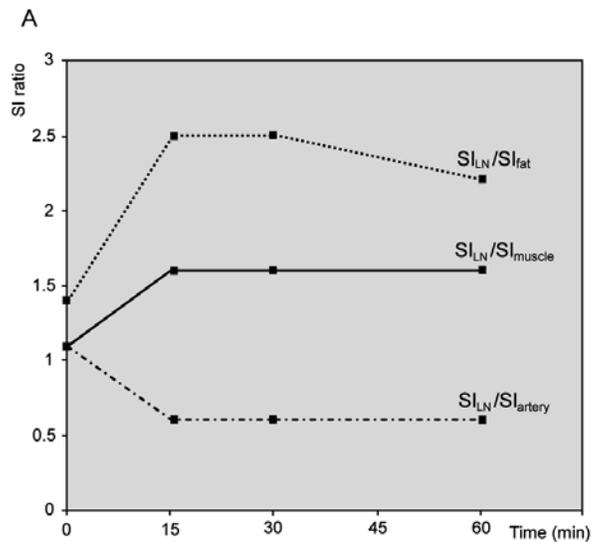


Fig. (1). Diagram of all lymph nodes depicted on MR images.

Taken as a whole, 56 nodes showed on both the 4D THRIVE and the 3D T1W GRE sequence a significant increase ($P < 0.01$) of signal intensity after Vasovist® administration.

The peak enhancement within the nodes was seen at 15 minutes after i.v. Vasovist® administration followed by a measured decrease of SI_{TN}/SI_{fat} ratio of $\Delta 0.3$ to 2.2 at 60 minutes using the 4D THRIVE sequence (Fig. 2 and 3).

The peak enhancement with the 3D T1W GRE sequence was depicted at 17 minutes after administration followed by a measured decrease of SI_{TN}/SI_{fat} ratio of $\Delta 0.2$ to 0.8 at 32 minutes (Fig. 4). A steadier pattern of signal intensity increase was seen with 3D T1-weighted images, illustrated by smaller standard deviations of the means.



B. 4D THRIVE sequence

	SI_{TN}/SI_{muscle}	P-value	SI_{TN}/SI_{fat}	P-value	SI_{TN}/SI_{artery}	P-value
T = 0	1.1 ± 0.4		1.4 ± 0.7		1.1 ± 0.7	
Vasovist Administration						
T = 15	1.6 ± 0.4	<0.01	2.5 ± 1.1	<0.01	0.6 ± 0.2	<0.01
T = 30	1.6 ± 0.4	<0.01	2.5 ± 1.1	<0.01	0.6 ± 0.2	<0.01
T = 60	1.6 ± 0.3	<0.01	2.2 ± 0.4	<0.01	0.6 ± 0.3	<0.01

Data are means \pm standard deviations
P-values were calculated for before and after Vasovist administration

Fig. (2). Diagram (A) and table (B) of the ratios SI_{TN}/SI_{muscle} , SI_{TN}/SI_{fat} and SI_{TN}/SI_{artery} at different time intervals using the 4D THRIVE sequence. The SI_{TN}/SI_{fat} ratio shows peak enhancement to 2.5 at 15 minutes, followed by a $\Delta 0.3$ gradual decrease to 2.2 at 60 minutes.

DISCUSSION

In general, the 4D THRIVE and the 3D T1W GRE sequence demonstrated a statistical significant increase of signal intensity within the node after Vasovist® administration.

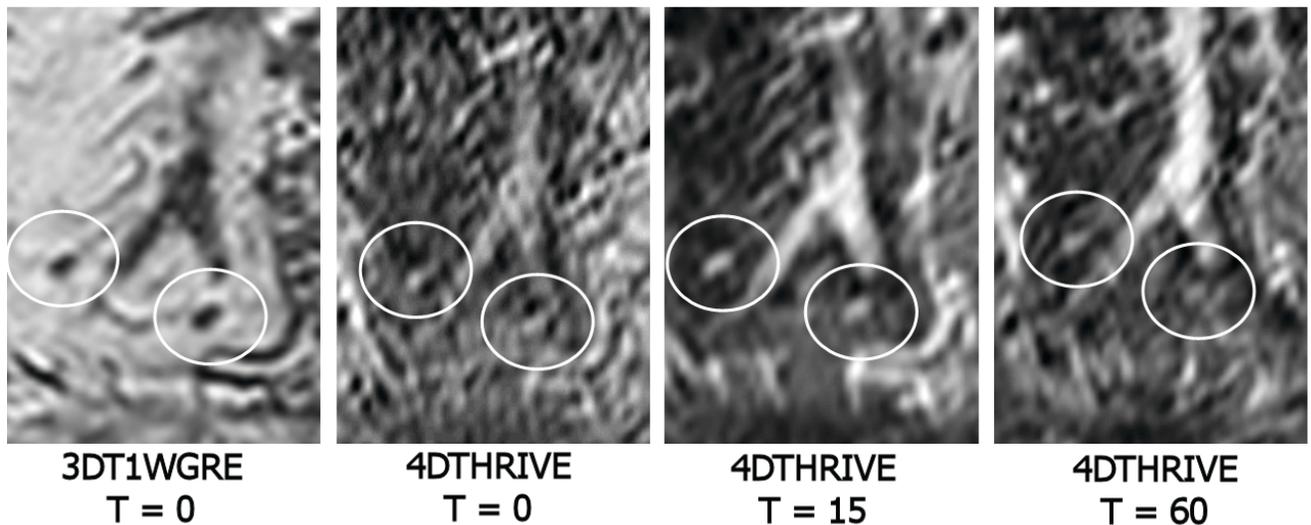


Fig. (3). Gradual enhancement of Vasovist® on 4D THRIVE images in two mesorectal nodes (white circles) in time. At T = 60 the nodes have a less bright signal intensity than at T = 15 minutes.

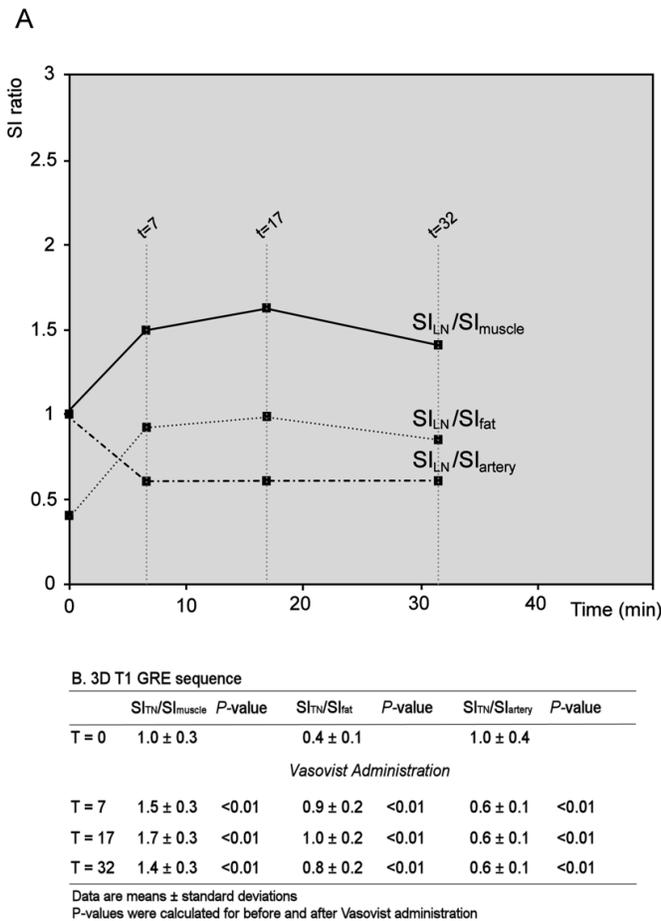


Fig. (4). Diagram (A) and table (B) of the ratios SI_{TN}/SI_{muscle} , SI_{TN}/SI_{fat} and SI_{TN}/SI_{artery} at different time intervals using the 3D T1W GRE sequence. The SI_{TN}/SI_{muscle} and SI_{TN}/SI_{fat} ratios show peak enhancement to 1.0 at 17 minutes, followed by a $\Delta 0.2$ gradual decrease to 0.8 at 32 minutes.

Although only little differences between the means at different time intervals were measured, both sequences showed a

peak enhancement in lymph nodes at 15 minutes after intravenous Vasovist® administration using the 4D THRIVE sequence and at 17 minutes using the 3D T1W GRE sequence. This signal increase in the lymph node was seen in 39 of the 41 nodes found in N0 patients. This suggests that Vasovist® is taken up by normal lymph node tissue increasing the signal intensity within the node. On the other hand no peak enhancement was seen in 6 of the 15 nodes found in patients with malignant nodes. These six lymph nodes are likely to have other than normal lymph node tissue and the absence of signal intensity increase could suggest replacement of nodal tissue by tumor tissue (Fig. 5).

The peak enhancement at 17 minutes was depicted using the SI_{TN}/SI_{muscle} and SI_{TN}/SI_{fat} with the 3D T1W GRE sequence. The SI_{TN}/SI_{artery} ratio cannot be used to measure Vasovist® enhancement within nodes, because the signal intensity increase in the nodes pales before the drastically increase of the signal intensity in the artery (SI_{artery}) as a result of the bloodpool effect of Vasovist®.

The most useful MR sequence is the 3D T1W GRE sequence, because of its superior resolution compared to the 4D THRIVE sequence. The 3D T1W GRE uses no turbofactor so that longer echo times can be applied. As a result there is a higher signal-to-noise ratio making small isotropic voxels possible. Furthermore the 4D THRIVE sequence makes use of a fat suppression technique leading to a further loss in anatomical detail. A lymph node that does not enhance with Vasovist® does not show a peak increase in signal intensity and will remain undetected among the hypointense mesorectal fat.

CONCLUSIONS

In conclusion this study shows that (i) intravenously administered Vasovist® shows enhancement in normal lymph nodes in rectal cancer patients, (ii) the optimal time of peak of enhancement after i.v. administration of Vasovist® is at 15 minutes (4D THRIVE) and at 17 minutes (3D T1W GRE) and (iii) the most optimal MR sequence to depict mesorectal lymph nodes in rectal cancer patients seems to be a 3D T1W GRE sequence.

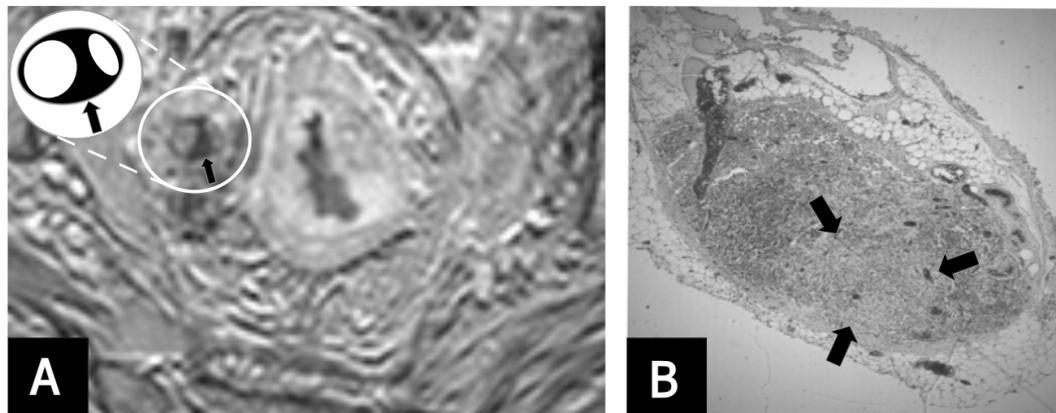


Fig. (5). (A) 3D T1W GRE image in the axial plane of the pelvis in a rectal cancer patient with a lymph node (white circle) 17 minutes after Vasovist® administration. No Vasovist® enhancement is seen in a part of the lymph node (arrow). Although no exact lesion by lesion analysis was performed in this feasibility study, (B) this node could match the only node with a tumor deposit (arrows) found in the same patient at the histopathological examination.

An accurate and extensive lesion by lesion analysis is however mandatory to investigate the accuracy of Vasovist[®] for predicting nodal metastasis and to develop consistent criteria to distinguish malignant from benign nodes. This will be the next step to do because if a gadolinium compound will prove to be as efficient as an iron oxide based compound in the prediction of nodal metastases in rectal cancer, it could become a promising alternative to USPIO, because of the less intensive and less cumbersome way of administration.

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