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ORIGINAL ARTICLE

Detection of lymph node metastases with ultrasmall superparamagnetic iron oxide (USPIO)-enhanced magnetic resonance imaging in oesophageal cancer: a feasibility study

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Abstract

Aim: In this feasibility study we investigated whether magnetic resonance imaging (MRI) with ultrasmall superparamagnetic iron oxide (USPIO) can be used to identify regional and distant lymph nodes, including mediastinal and celiac lymph node metastases in patients with oesophageal cancer.

Patients and methods: Ten patients with a potentially curative resectable cancer of the oesophagus were eligible for this study. All patients included in the study had positive lymph nodes on conventional staging (including endoscopic ultrasound, computed tomography and fluorodeoxyglucose-positron emission tomography). Nine patients underwent MRI + USPIO before surgery. Results were restricted to those patients who had both MRI + USPIO and histological examination. Results were compared with conventional staging and histopathologic findings.

Results: One patient was excluded due to expired study time. Five out of 9 patients underwent an exploration; in 1 patient prior to surgery MRI + USPIO diagnosed liver metastases and in 3 patients an oesophageal resection was performed. USPIO uptake in mediastinal lymph nodes was seen in 6 out of 9 patients; in 3 patients non-malignant nodes were not visible. In total, 9 lymph node stations (of 6 patients) were separately analysed; 7 lymph node stations were assessed as positive (N1) on MRI+USPIO compared with 9 by conventional staging. According to histology findings, there was one false-positive and one false-negative result in MRI + USPIO. Also, conventional staging modalities had one false-positive and one false-negative result. MRI + USPIO had surplus value in one patient. Not all lymph node stations could be compared due to unforeseen explorations. No adverse effects occurred after USPIO infusion.

Conclusion: MRI+USPIO identified the majority of mediastinal and celiac (suspect) lymph nodes in 9 patients with oesophageal cancer. MRI+USPIO could have an additional value in loco-regional staging; however, more supplementary research is needed.

Keywords: *oesophageal cancer; oesophagectomy; lymph node staging; ultrasmall superparamagnetic iron oxide (USPIO)-enhanced magnetic resonance imaging (MRI).*

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Introduction

An oesophageal resection for cancer is a major surgical procedure associated with substantial peri-operative morbidity (40–50%) and mortality (2–15%)[1]. To determine resectability in these tumours, adequate staging is essential, selecting only those patients who may benefit from curative surgery[2,3]. Anatomical staging of these tumours is usually performed in specialized institutes by endoscopic ultrasonography (EUS) plus fine-needle aspiration (FNA) and computed tomography (CT) of the neck, chest and abdomen[4]. However, traditional methods for staging oesophageal cancer have limited sensitivity and specificity. The incidence of missed distant lymph node metastases prior to surgery not detected by conventional imaging techniques is relatively high (10–38%)[5,6]. Because anatomic imaging (CT, EUS+FNA) primarily depends on the size of lymph nodes, frequently found nodal metastases that are not enlarged are missed[7]. Furthermore, FNA can be very difficult to perform due to unreachable lymph nodes or indistinct determination of malignant nodes by EUS. Moreover, suspected lymph nodes can be situated behind the primary tumour, so the endoscopist has to puncture through the tumour to reach the lymph node, with a high chance of false-positive results. Therefore, better pre-operative staging is warranted to prevent unnecessary explorative surgery in this group of patients.

^{18}F-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) has become a conventional pre-operative staging modality for oesophageal cancer. However, it is primarily used for the detection of distant lymph node adenopathy and haematogenous metastases (M1a/b) because of the low sensitivity (30–50%) for detection of local malignant lymph nodes[8,9]. Moreover, false-positive results may occur due to an increased glucose metabolism in benign lesions[10]. The drawback of FDG-PET is the lack of anatomical information on the metastases detected, which can be partially solved by using the combination of PET/CT[11].

Recently, magnetic resonance (MR) imaging with ultrasmall superparamagnetic iron oxide (USPIO) is gaining acceptance as a non-invasive method for the detection of lymph node metastases in several tumours[12–19]. MR provides images with excellent anatomical detail and soft tissue contrast but at the same time is relatively insensitive to lymph node metastases due to the limited sensitivity of current node size criteria in differentiating benign from malignant nodes[12]. However, the MR results can be improved by using a superparamagnetic contrast such as USPIO[20,21]. USPIO acts as a negative contrast agent and therefore normal functioning lymph nodes can be distinguished from lymph node metastases on the basis of magnetic resonance signal characteristics, independent of nodal size[16,17,21,22].

High sensitivities ranging from 81 to 100%, specificities ranging from 77 to 98% and accuracies ranging from 86 to 95% have been reported for MR + USPIO lymph node staging for different types of tumours[12–15,22–24]. These encouraging results warrant further investigation in oesophageal cancer with its early and unpredictable pattern of nodal spread.

This feasibility study was designed to assess the value of MR enhanced with USPIO for the detection of lymph nodes and staging of nodal metastases in oesophageal cancer. The main objective was to investigate whether USPIO can be used to detect both regional and distant lymph nodes and nodal metastases, in patients with oesophageal cancer, and, furthermore, whether MR alone or enhanced with USPIO could visualize these lymph node metastases, including mediastinal and celiac lymph nodal metastases. The results of MR with USPIO were compared with the conventional staging results (EUS, CT, FDG-PET) and with routine histological findings as the gold standard.

Patients and methods

Patients

Ten patients with potentially resectable cancer of the oesophagus or gastro-oesophageal junction were eligible for this study. All patients were selected on clear mediastinal and/or celiac nodal involvement (N1 or M1a) as determined by conventional staging modalities (EUS, CT, PET), to ensure comparison of normal nodes and nodal metastases for MR + USPIO with other staging procedures and pathology. CT and EUS assessed lymph nodes on size and morphology. Nodes with a size >10 mm and/or irregular shape were suspected for malignancy, nodes with a size of 5–10 mm were scored as possible malignancy. Staging on PET was performed by standard staging protocols for standard uptake value and based on the experience of the nuclear medicine physician.

Patients were able to tolerate MRI, USPIO infusion and oesophagectomy. MRI and USPIO infusion was performed after evaluation of conventional staging modalities and approximately 1 week before surgery. Exclusion criteria were: known allergies to dextran or iron-containing compounds, age <18 years, pregnancy, previous treatment for oesophageal cancer, claustrophobia, aneurysm clips, pacemakers or artificial heart valves. One patient had to be excluded due to expired study time of the USPIO contrast. In the remaining 9 patients we evaluated the impact of USPIO-enhanced MRI in detecting lymph node metastases in oesophageal cancer. None of these patients received neo-adjuvant treatment.

Ultrasmall superparamagnetic iron oxide (USPIO) contrast

The lymphotropic superparamagnetic nanoparticles used in this study were a monocrystalline iron oxide made of

biodegradable particles, dextran and sodium citrate (Sinerem, Guerbet, Paris, France)[25]. The nanoparticles are composed of an iron oxide crystalline core 5 nm in diameter and are covered with low molecular weight dextran. The lyophilized iron oxide powder was reconstituted in normal saline (10 ml) and injected in 100 ml saline fluid. Based on the results of a dose-ranging study, the solution was infused intravenously, through a filter, at a rate of 4 ml/min over a period of approximately 30 min, 24–36 hours before MR, at a dose of 2.6 mg of iron per kilogram of body weight (0.13 ml/kg)[26].

After intravenous administration, USPIO particles reach lymph nodes by two distinct pathways (Fig. 1). The major pathway is that of direct transcapillary passage through high endothelial venules within individual lymph nodes. Once within the nodal parenchyma, phagocytic cells of the mononuclear phagocyte system engulf the particles. The second pathway is through nonselective endothelial transcytosis across permeable capillaries throughout the body into the interstitium. USPIO particles are subsequently taken up from the interstitium by lymphatic vessels and transported to regional lymph nodes[20,27].

A lymph node with normal phagocytic function takes up a substantial amount of USPIO and therefore markedly reduces the signal intensity following intravenous administration of iron oxide agents secondary to the magnetic susceptibility and T2* shortening effects of the iron oxide particles[12]. In metastatic lymph nodes, tumour cells replace the normal cells. This results in a decrease in the number of macrophages and can therefore result in a decrease in the uptake of a lymph node-specific tracer and maintains relatively high signal intensity[28].

The most frequently reported adverse events in the literature are headache, back pain, vasodilatation and urticaria, each of which occur in 6% of patients[12,13,28]. No serious adverse events have been reported. Possible adverse effects were examined verbally and clinically during USPIO infusion and 24 hours after infusion. During the infusion of USPIO, a physician was present to watch over the process and detect possible adverse effects.

Magnetic resonance (MR)

MRI was performed with a 1.5 T unit (Siemens Sonata). T1, T2 and T2* (gradient echo) transverse and coronal images of the cervical region and thorax and upper abdomen were obtained before and 24–36 hours after the intravenous administration of USPIO. MRI sequence parameters are listed in Table 1. After surgery, the resection specimens, or in the case of non-resectability excised lymph nodes, were fixated on a grid with anatomical

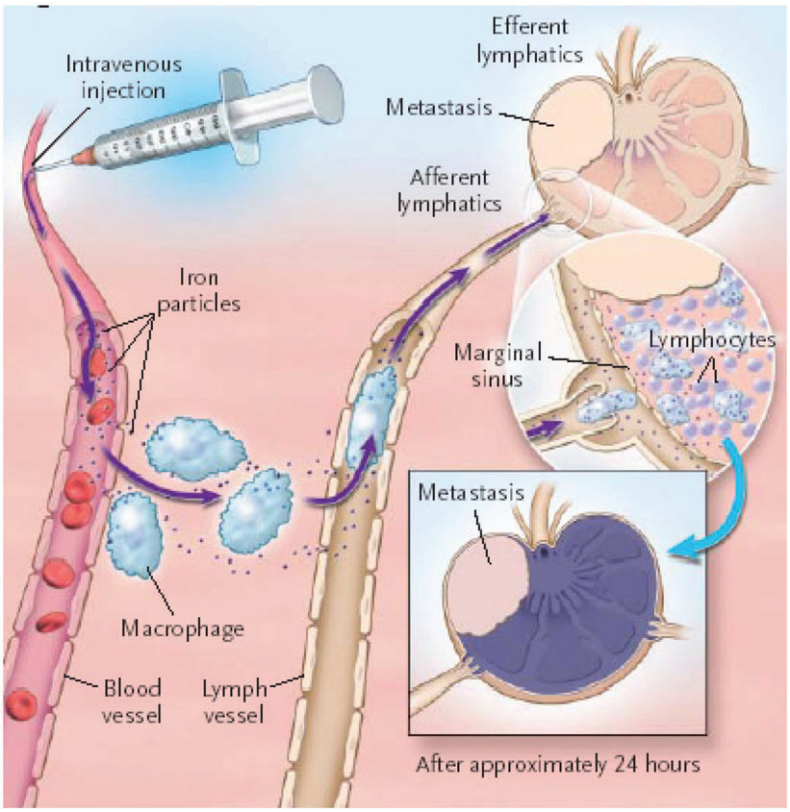

Figure 1 **Schematic pathway of USPIO uptake in lymph nodes: reproduced with permission from Harisinghani et al. NEJM 2003[13].**

Table 1 MRI sequence parameters

Cervical/thorax:			
T2-TSE-tra-fs	T2-Fl2D-tra-we	T1-MPRage-tra-fs	T2-Fl2D-cor-we
TR 5100	327	1840	236
TE 104	4,76	4,38	4,76
FOV 250	280	280	350
Slice 5	5	1,7	5
Matrix 320*288	320*288	256*256	320*288
Voxel 0,9*0,8*5	1*0,9*5	1,1*1,1*1,7	1,2*1,1*5
Thorax/abdomen:			
T2-TSE-tra-FrBr	T2-fl2D-tra-FrBr	T1-VIBE-tra-fs-bh	
TR 1490	1530	4,78	
TE 87	4,08	2,26	
FOV 360	360	350	
Slice 5	5	2	
Matrix 384*269	256*192	256*166,5	
Voxel 1,3*0,9*5	1,9*1,4*5	2,1*1,4*2	

landmarks, and scanned *ex vivo* with T2* sequences. These results were compared with MRI + USPIO *in vivo*.

Image analysis

The MR images were evaluated independently by an experienced MR radiologist who was blinded for outcome of conventional staging modalities, surgical outcome and histopathalogic examination. These MR + USPIO results were compared with the histopathological findings of the pathologist.

In MRI with lymphotropic superparamagnetic nanoparticles, nodes were considered malignant when one of the following criteria were present: a decrease in signal intensity of more than 30% on T2-weighted fast spin–echo or gradient-echo sequences; a heterogeneous signal (giving the entire node a mottled appearance), discrete focal defects (isolated islands of high signal intensity), or both; and nodes with a central area of hyperintensity (excluding a fatty hilum) but a peripheral decrease in signal intensity (Fig. 2)[13]. The signal-to-noise ratios of lymph nodes were determined by manually marking regions of interest over lymph nodes on different scans and pulse sequences. Diagnostic procedures were evaluated by histopathological examination of each lymph node according to the fixated anatomical localization (Fig. 3). Histopathology was considered to be the gold standard.

Surgery

In the 9 eligible patients, the peritoneal cavity was first explored to exclude metastatic disease. In the case of peritoneal carcinomatosis, hepatic metastases and bulky nodal involvement of >2 cm within 1 cm of the celiac region (M1), resection was not performed after histological confirmation (frozen section). In these cases we attempted to remove the relevant lymph nodes on the basis of MRI results. If the above-mentioned nodes were not involved, a radical resection with curative intent was performed. Standard oesophageal resection consisted of either a distal oesophagus/cardia resection through a left thoraco-laparotomy with intrathoracic anastomoses or a subtotal oesophageal resection through a right thoraco-mid-laparotomy with cervical anastomoses. Both were combined with a two-field lymphadenectomy of mediastinal nodes and abdominal nodes, including those at the celiac trunk, upper border of the pancreas and para-aortic region. Based on the results of the USPIO-enhanced MRI, suspected lymph nodes were included.

To match the MR imaging to the *ex vivo* lymph nodes, a fixation method was used to interpret the lymph node groups according to Fig. 3. The resection specimen was pinned in a polycarbonate box with a grid and a transparent cover to keep anatomical survey possible (Fig. 4). On this box, the locations of (suspected) nodes were carefully marked and described by the surgeon to make the comparison with all MR images (MRI, MRI+USPIO and MRI of *ex vivo* resection specimen) and pathology.

Histology

All independent lymph nodes found during pathology were marked by their anatomical position and compared by individual lymph nodes on MR. Lymph nodes were examined histologically according to the standard histological procedures. Adenocarcinoma seen on hematoxylin and eosin staining was, in all cases, confirmed by ceratin staining (immunohistochemical analysis).

Data analysis

Due to the unforeseen explorations, evaluation of the final results was restricted to those patients who had both MRI + USPIO and histological examination. For this feasibility study, only descriptive and correlation statistics were used. The results of this feasibility study will provide enough information to assess the potential use of USPIO-enhanced MR for detecting and staging

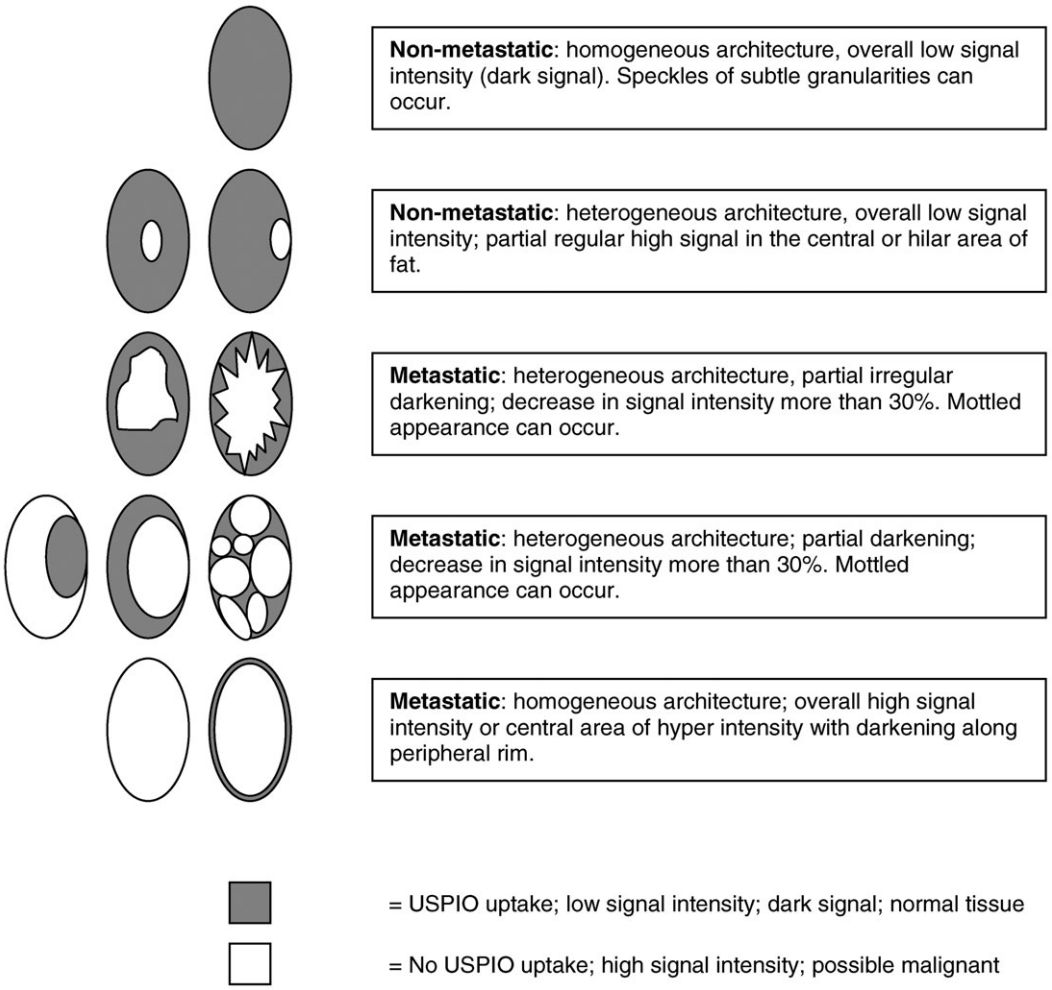

Figure 2 **Schematic diagnostic guidelines for USPIO-enhanced MR imaging. Nodes are considered malignant when one of the following criteria are present: a decrease in signal intensity of less than 30% on T2-weighted fast spin-echo or gradient-echo sequences after the administration of USPIO; a heterogeneous signal (giving the entire node a mottled appearance), discrete focal defects (isolated islands of high signal intensity), or both; and nodes with a central area of hyperintensity (excluding a fatty hilum) but a peripheral decrease in signal intensity.**

lymph node metastases in oesophageal cancer patients in future clinical studies.

Medical ethics

This study was conducted according to the principles of the Declaration of Helsinki 1975, and its subsequent revisions, and in accordance with the principles of Good Clinical Practice and the Medical Research Involving Human Subjects Acts. The study was approved by the Medical Ethical Committee of our university hospital. Patients were informed about the purpose and hazards of the study, both orally and in writing, and gave their written informed consent.

Results

All 9 patients were staged pre-operatively as N1 and/or M1a oesophageal adenocarcinoma with conventional staging modalities (including EUS, CT and FDG-PET). Patient characteristics are summarized in Table 2. Six out of 9 patients had no resection due to extensive lymph node involvement or unexpected distant metastases.

One patient appeared to have liver metastases which were observed on the pre-operative MRI + USPIO, and which was confirmed by additional abdominal ultrasonography. Subsequently, percutaneous biopsies revealed metastases (adenocarcinoma). This patient was therefore excluded from surgery.

During the operation, 1 patient appeared to have histologically proven pleural metastases, another patient had a T4 tumour with ingrowth at the left main bronchus. Another patient had unforeseen growth of the tumour into the wall of the abdominal aorta and diaphragm, with suspected lymph nodes in the hepatoduodenal ligament. Three patients had previously undetected liver

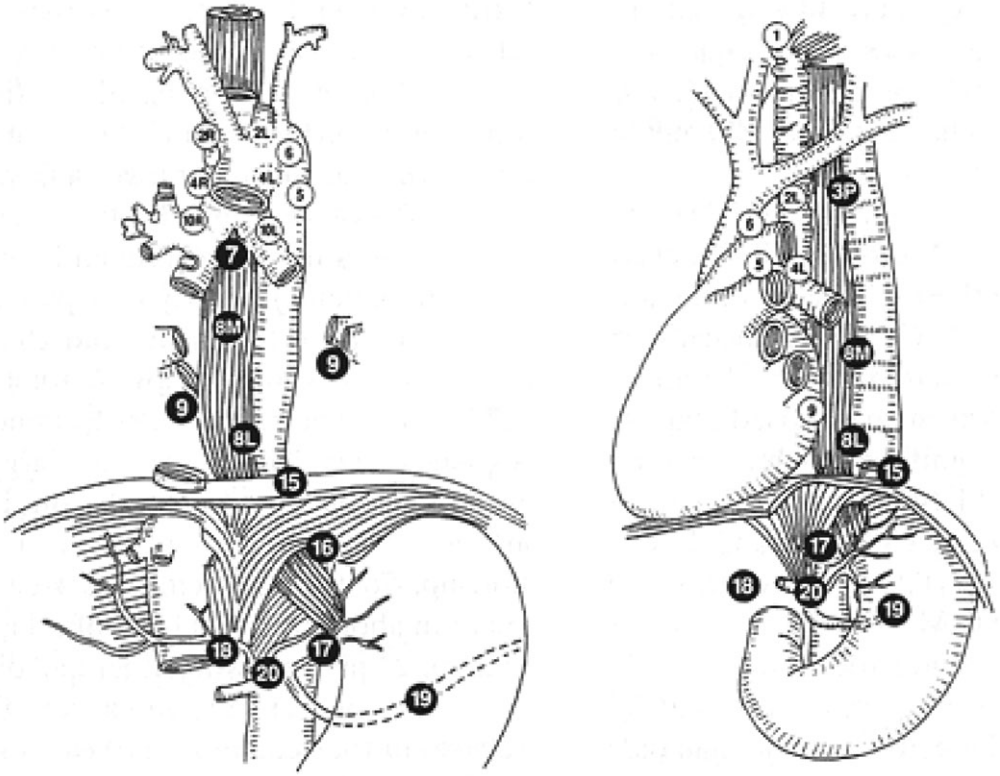

Figure 3 **Anatomical localization of lymph node stations. According to the American Joint Committee on Cancer (AJCC), Cancer Staging Manual, Sixth edition (2002).**

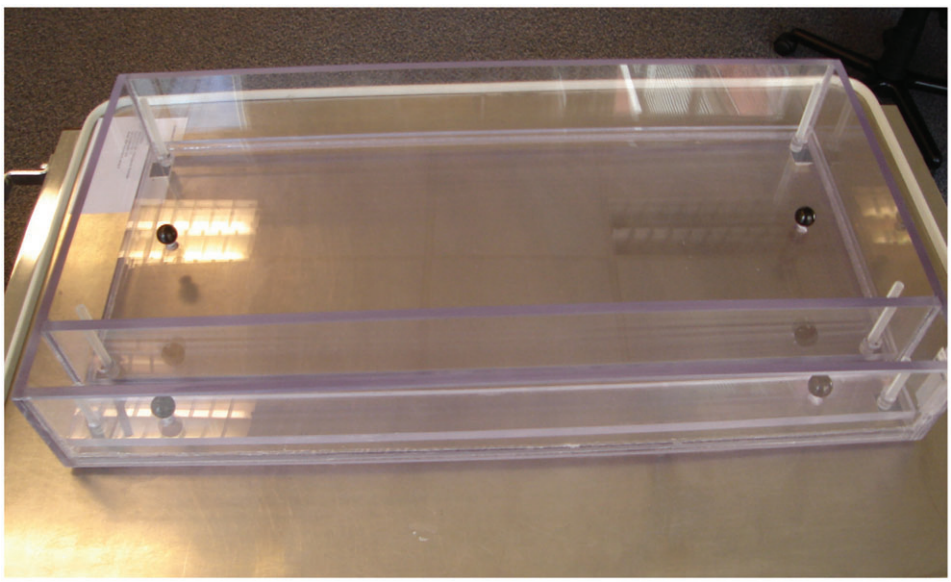

Figure 4 **Polycarbonate fixation box with cover and grid to keep the *in vivo* anatomical position of the resection specimen for *ex vivo* MRI and histological examination intact. Remarks, number of lymph nodes and anatomical location were marked on the transparent cover, above the fixated specimen. Separate lymph nodes were fixated at the side with exact described anatomical location by the surgeon.**

metastases; two small lesions (<0.5 cm) were histologically proven during exploration. During two explorative procedures lymph node samples were taken of the MRI + USPIO suspected lymph nodes for histological conformation. The remaining 3 patients underwent a standard oesophageal resection with a post-operative control MRI of the resected specimen followed by histopathological examination.

Because of the five explorations and 1 patient with liver metastases prior to surgery, histology was not acquired for interpretation of two MRI + USPIO diagnosed lymph node stations. Therefore, no outcome can be given between the comparison of standard modalities and MRI + USPIO in these two lymph node stations. In other explorations, lymph node stations suspected by conventional and MRI + USPIO staging were (partially) dissected to obtain histology.

Table 2 Patient characteristics

Total number	9
Gender (%)	
Male	9 (100)
Female	0
Age (years)	
Median	59
Range	51–69
Localization (%)	
Distal oesophagus	6 (66.7)
GEJ	3 (33.3)
Histology (%)	
Adenocarcinoma	9 (100)
Squamous cell carcinoma	0

Identification of lymph nodes on MRI alone was not comparable with conventional staging, especially in small and irregular nodes on CT. These small nodes were identified after USPIO infusion with T2* MRI, although spatial resolution is slightly less than on CT. USPIO uptake was seen in 6 out of 9 patients in several abdominal and mediastinal lymph node stations (Fig. 5a–c and Fig. 6a,b); in 3 patients non-malignant nodes were not visible with USPIO. Out of the 6 patients with USPIO uptake, in total 9 lymph node stations were analysed. These 9 lymph node stations were compared with conventional staging modalities whereby histological examination was the gold standard. The following stations were assessed as positive (N1): 7 lymph node stations on

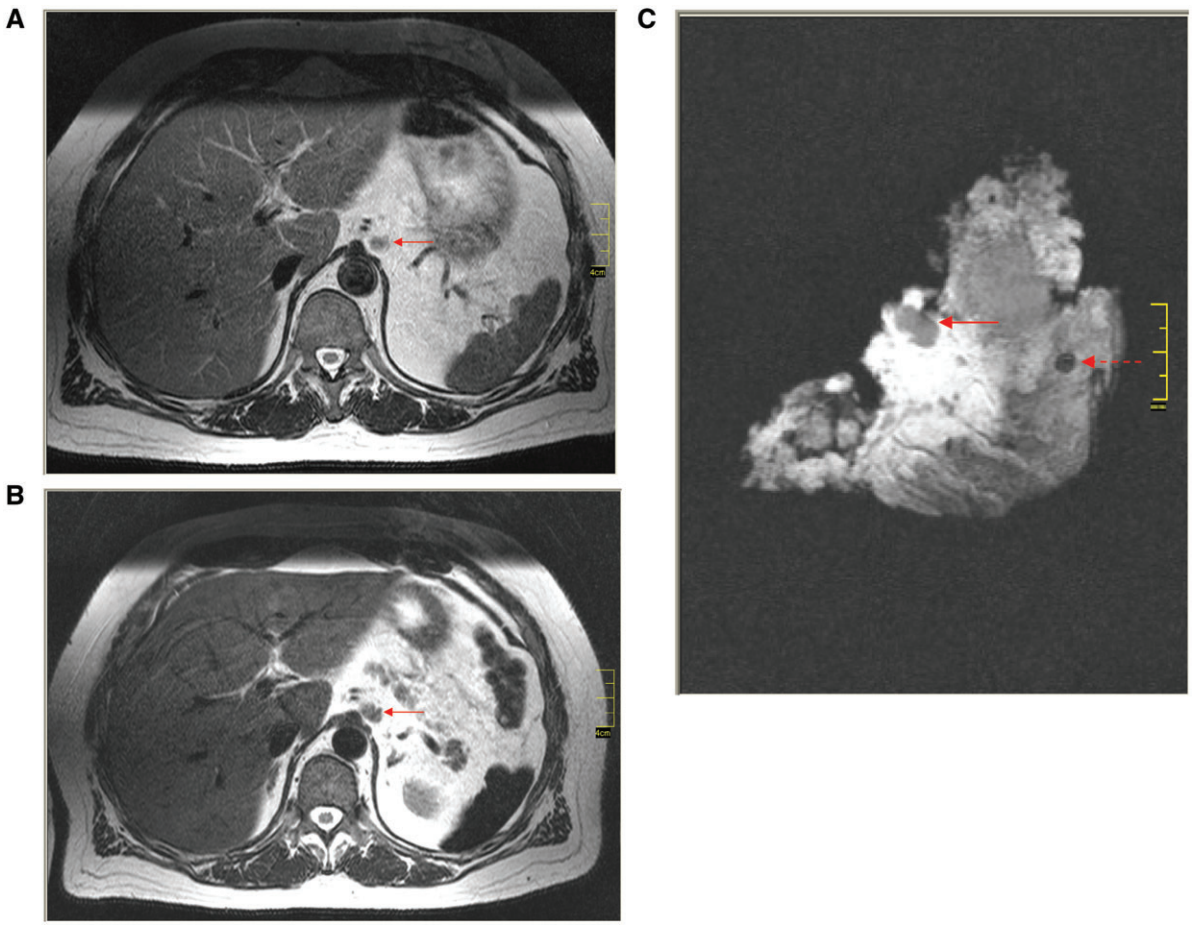

Figure 5 **(A) Pre-enhanced MR image of patient 02 (T2* without USPIO); indicated lymph node (←—); (B) USPIO-enhanced MR imaging T2* of patient 02; no USPIO uptake in indicated (←—) lymph node which corresponds with Fig. 5A. Other lymph nodes in this series demonstrated USPIO uptake. (C) USPIO-enhanced MR T2* image of resection specimen (distal oesophagus and part of the cardia with fatty tissue and lymph nodes along the minor curvature) of patient 02 with corresponding lymph node as in Fig. 5A + B (←—). Note the USPIO uptake in marked histology proven negative lymph node (←---) and no USPIO uptake in histology proven positive lymph node (←—).**

Table 3 Results of conventional staging and MR + USPIO versus histopathology in the 6 patients with USPIO uptake

USPIO	Lymph node station	Conventional staging	MRI USPIO staging	Pathology	Outcome conventional staging	Outcome USPIO	Remarks
01	17	+	+	+	P	P	exploration
	8	+	−	#			
02	8	+	+	−	FP	FP	
	16/17	+	+	+	P	P	
03	8/9	+	+	+	P	P	exploration
04	8	+	−	+	P	FN	
	17	−	+	+	FN	P	
06	16/17	+	+	#			exploration
08	7/8	+	+	+	P	P	

USPIO: Patient study number (01–09). Lymph node station: number of lymph node station(s) according to Fig. 3. Conventional staging: staging based on conventional staging modalities (CT/PET/EUS) and multidisciplinary consultation. MRI USPIO staging: staging of related lymph nodes according to USPIO uptake (+ = no USPIO uptake in corresponding lymph node, suspect for malignancy). Pathology: staging based on histology findings of corresponding lymph node (gold standard) # = no histology available. Outcome conventional staging P = positive finding, FP = false-positive, FN = false-negative. Outcome USPIO: P = positive finding, FP = false-positive, FN = false-negative.

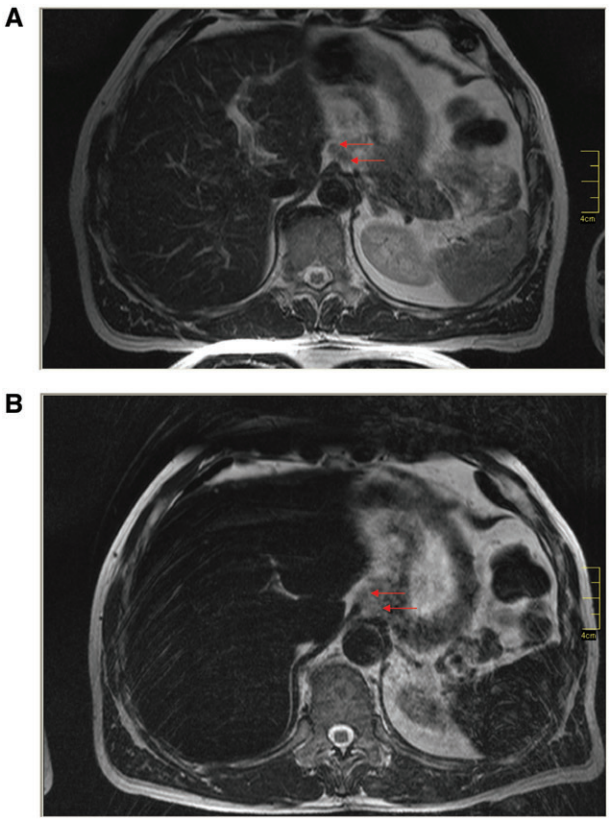

Figure 6 **(A) Pre-enhanced T2* image of patient 08. Note two indicated lymph nodes; (B) USPIO-enhanced T2* image of patient 08. Note two indicated lymph nodes without USPIO uptake which were proven positive on histopathologic findings.**

MRI + USPIO and 9 stations on conventional staging modalities (Table 3).

Histology was only available in 7 lymph node stations due to the unforeseen explorations. Five of these 7 (83.3%) lymph node stations were proven positive (N1) by histology findings (Fig. 7).

For conventional staging, there was one false-positive and one false-negative result according to histology. For

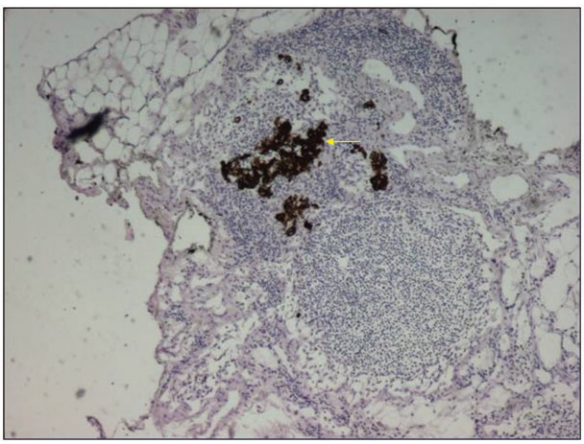

Figure 7 **Partial lymph node with metastatic adenocarcinoma tissue, proven by ker Ae1/3 immunohistochemical staining (black staining←) of patient 02 with corresponding MR + USPIO suspected malignant lymph node.**

MRI + USPIO there was also one false-positive and one false-negative finding. One of the false-positive lymph nodes, according to histology, was positive on MRI + USPIO as well as conventional staging. One station was missed by all conventional staging modalities and positive on MRI + USPIO, which was confirmed by histology examination.

In comparison with MRI + USPIO *in vivo* and postoperative MRI of the resected specimen, more negative lymph nodes were seen *ex vivo* on the MRI. There was no increase in positive lymph nodes seen on MRI + USPIO *ex vivo*. Furthermore, the number of histology-proven positive lymph nodes did not differ.

All patients received the full dose USPIO and completed the entire study. The average total MRI examination time of 1 hour was well tolerated in all cases. No adverse effects were encountered in the 9 patients included in the study, either during or after infusion of USPIO. The patients experienced no greater burden than with other staging modalities.

Discussion

In this feasibility study, USPIO uptake was seen in 6 out of 9 eligible patients. In 5 patients lymph node status was positive on conventional staging and MRI + USPIO, and was confirmed by histopathological examination. MRI + USPIO upstaged 1 patient according to standard staging modalities. Due to the pre-operative selection on nodal metastases, unfortunately only 3 patients underwent a resection and histology was only acquired in 5 patients (7 lymph node stations) due to unforeseen extensive cancer growth or metastases. This was the major drawback of this study and therefore these results might be an underestimation.

Identification of lymph nodes on MRI alone had no additional value, especially in small nodes on CT. These small nodes could be identified after USPIO infusion with T2* MRI, although spatial resolution is slightly less than on CT. No adverse effects were found by the infusion of USPIO and patients experienced no greater burden than with other staging modalities.

All patients in this study had adenocarcinoma. It is unclear if the same results for USPIO uptake would be found in patients with squamous cell carcinoma. We expect that there will be no difference in USPIO uptake in the lymph nodes for squamous cell carcinoma, because USPIO uptake is dependent on physical invasion of the nodes and not on physiological behaviour of the tumour cells. However, this question should be answered in forthcoming studies.

In 5 out of 9 patients current staging modalities missed local or distant metastases and resulted in a surgical exploration; a complete comparison by conventional modalities and USPIO-enhanced MRI could therefore not be made. This stresses the importance of finding new, adequate staging procedures and improving conventional diagnostic modalities. MRI enhanced with USPIO appears to be a good predictor of oesophageal lymph node staging. There was avid USPIO uptake in the majority of mediastinal and paragastric lymph nodes. MR + USPIO may have high potential value as a new non-invasive staging modality in oesophageal cancer. USPIO could be applied safely, is inexpensive in comparison with EUS and PET and its technique (MRI) is widely available. More research is needed to compare MRI + USPIO with current staging modalities and therefore we propose a diagnostic accuracy study with inclusion of all potentially curative patients on conventional staging modalities to assess its accuracy and efficacy.

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