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FULL PAPER

MRI sequences for the detection of individual lymph nodes in regional breast radiotherapy planning

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Objective: In regional radiotherapy (RT) for patients with breast cancer, lymph node (LN) targets are delineated on CT, defined by anatomical boundaries. By identifying individual LNs, MRI-based delineations may reduce target volumes and thereby toxicity. We optimized MRI sequences for this purpose. Our aim was to evaluate the techniques for LN delineation in RT planning.

Methods: Supine MRI was explored at 1.5 T in RT position (arms in abduction). 5 MRI techniques were optimized in 10 and evaluated in 12 healthy female volunteers. The scans included one T_1 weighted (T1w), three T_2 weighted (T2w) and a diffusion-weighted imaging (DWI) technique. Quantitative evaluation was performed by scoring LN numbers per volunteer and per scan. Qualitatively, scans were assessed on seven aspects, including LN contrast, anatomical information and insensitivity to motion during acquisition.

Results: Two T2w fast spin-echo (FSE) methods showed the highest LN numbers (median 24 axillary), high contrast, excellent fat suppression and relative insensitivity to motion during acquisition. A third T2w sequence and DWI showed significantly fewer LNs (14 and 10) and proved unsuitable due to motion sensitivity and geometrical uncertainties. T1w MRI showed an intermediate number of LNs (17), provided valuable anatomical information, but lacked LN contrast.

Conclusion: Explicit LN imaging was achieved, in supine RT position, using MRI. Two T2w FSE techniques had the highest detection rates and were motion insensitive. T1w MRI showed anatomical information. MRI enables direct delineation of individual LNs.

Advances in knowledge: Our optimized MRI scans enable accurate target definition in MRI-guided regional breast RT and development of personalized treatments.

INTRODUCTION

The standard treatment for patients with breast cancer with tumour-positive sentinel node(s) or clinical axillary lymph node (LN) metastasis is axillary LN dissection (ALND). ALND has been shown to cause arm morbidity in up to 60% of the patients, including arm oedema, shoulder pain and shoulder function restriction.^{1,2} In patients with tumour-positive sentinel node(s), ALND is increasingly being omitted or replaced by regional radiotherapy (RT) based on recent results of the American College of Surgeons Oncology Group Z0011 study and the European Organization for Research and Treatment of Cancer After Mapping of the Axilla: Radiotherapy or Surgery? trial.^{3–8} In the latter, no difference was observed in regional recurrence rate, with decreased arm oedema in the RT group. RT-induced toxicity of all grades occurred in a median 14% of the patients.⁶

Standard regional RT comprises irradiation of the LNs in the axilla with or without the supraclavicular area ±

internal mammary LNs. Conventionally, these LN areas are delineated on CT scans. The contouring is performed following delineation guidelines defined by anatomical boundaries, since most LNs cannot be visualized with CT.^{9–11} As a consequence, target volumes are relatively large (Figure 1), resulting in large high-dose volumes in normal tissue, such as muscles, brachial plexus, lungs, heart and connective tissue.^{6,12–15} Complications associated with regional RT include arm oedema, decreased arm mobility, brachial plexopathy and radiation pneumonitis.

More accurate target delineation could be achieved by more explicit LN imaging than currently achievable with CT. Direct visualization of regional LNs in relation to their surrounding organs at risk is of utmost importance to accomplish a higher accuracy. Owing to its superior soft-tissue contrast in particular, MRI may be more useful than CT in this aspect¹⁶ and could facilitate individual LN

Figure 1. Example of standard axillary delineations on CT in a patient with breast cancer in radiotherapy (RT) position. A transverse slice of the CT scan is shown (left), with the corresponding coronal view (right). Inner line is the clinical target volume (CTV) of the lower axilla for standard right-sided axillary RT; outer line is the planning target volume (not indicated in the figure), which is generated by an expansion of the CTV by 5 mm isotropic. Target delineations are performed based on guidelines with the use of anatomical boundaries. As a consequence, target volumes are relatively large. Other delineated structures are the ipsilateral lung, contralateral lung and heart.

delineation. Potentially, the implementation of MRI in RT planning may lead to smaller treated volumes.

Previous studies on LN imaging indicate an added value of diagnostic MRI for several anatomical locations, including the axilla.^{17–22} However, conventional diagnostic MRI techniques for patients with breast cancer are not suitable for regional RT planning. Conventional techniques are not optimized for visualization of all LNs, as they are primarily developed for imaging and staging of the tumour. Secondly, the scanning position is prone, which differs from the RT position, *i.e.* supine with abducted arms. Furthermore, diagnostic MRI scans for the breast are usually T_1 weighted (T_1w) images. As a result, on these images, LNs lack contrast with surrounding tissues and, as such, can go unnoticed. Additionally, since a breast coil is used conventionally, which does not cover the entire regional area, not all regional LNs are imaged. For these reasons, dedicated MRI techniques in supine RT position are required to be suitable in regional RT planning.

Accurate LN visualization using MRI is challenging, since several aspects need to be taken into account in the design of pulse sequences capable of making regional LNs visible. These elements include contrast of LNs relative to the surrounding tissue, resolution, geometric accuracy, sensitivity to motion during scan acquisition and visibility of anatomical reference structures. Moreover, methods to suppress fat and blood signal are required to distinguish LNs from fatty tissue and nearby blood vessels. In particular, the success of fat suppression techniques can be influenced by the scanning position.

Since the aim of regional RT is to irradiate all regional LNs in the target area, the MRI technique should have a high sensitivity to detect individual LNs. To our knowledge, no previous study has been published which focused on MRI in supine RT position for this goal. In 10 healthy volunteers, we have designed and optimized 5 clinically applicable MRI sequences to visualize individual axillary and supraclavicular LNs. Evaluation of these

techniques is performed in another 12 healthy female volunteers. The objective of this work was to establish which MRI sequences best facilitate LN delineation in RT planning.

METHODS AND MATERIALS

All participants provided their written informed consent to participate in the study. The Internal Review Board of the University Medical Center (UMC) Utrecht, Utrecht, Netherlands, approved this procedure. Scanning was performed at the Radiology and RT Department of UMC Utrecht from 2013 to 2015.

Volunteers and scanner setup

5 MRI sequences were developed and optimized on image quality and scan time in 10 healthy female volunteers, whose age ranged from 24 to 54 years. Subsequently, in 12 additional female volunteers, the optimized MRI scans were applied for evaluation. Age of the final 12 volunteers ranged from 23 to 49 years, and the range of their body mass index ($BMI = \text{weight}/\text{length}^2$) was $19.4\text{--}31.2 \text{ kg m}^{-2}$. The subjects were scanned on a wide-bore 1.5-T Ingenia MRI scanner (Philips, Best, Netherlands) in supine position, with a knee support. A 10° Thorawedge board (CIVCO Medical Solutions, Reeuwijk, Netherlands) was used, and both arms were in abduction, resting on the board (RT position). An anterior FlexCoverage receive coil (Philips) was connected, placed on a custom-made, adjustable polymethyl methacrylate support to avoid deformation of the outer body contour and secured to the table. A posterior receive coil (Philips) was situated in the patient table of the scanner (Figure 2). No contrast agent was administered.

In total, the MRI scanning protocol was restricted to 20 min. Additional time in supine RT position of up to 10 min was required for subject positioning and scanning preparation. Endurance was monitored by noting whether a volunteer could finish the entire MRI scanning procedure without physical problems (*e.g.* pain in shoulder or arms). If not, the reason of insufficient endurance was noted.

Figure 2. MRI scanning setup. The volunteer is placed on a 10° Thorawedge board (CIVCO Medical Solutions, Reeuwijk, Netherlands) in supine RT position, i.e. with arms in abduction, resting on the board. Scanning is performed with a 1.5-T Ingenia (Philips, Best, Netherlands) wide-bore MRI scanner. An anterior FlexCoverage (Philips) receive coil is connected and placed on top of a custom-made polymethyl methacrylate support, which is adjustable, in order to prevent deformation of the outer body contour. A posterior receive coil (Philips) is located in the table.

MRI scans

The optimized MRI scans included two-dimensional and three-dimensional (3D) sequences. The field-of-view for all scans was chosen to cover the breast, and the axillary and supraclavicular regions up to the mandible and was 250, 420 and 100 mm in caudal–cranial, right–left and anteroposterior directions, respectively. All images were acquired in the coronal plane.

Clinical applicability was established by limiting the scan duration to a maximum of 7 min per scan. Relevant scan parameters are summarized in Table 1.

The sequences included a T1w 3D spoiled gradient echo technique or T1w fast field echo (T1-FFE). Water-only images from multipoint Dixon (mDixon) fat separation could be generated with the T1-FFE technique, which shows similar contrast of soft tissues to CT scans used for standard RT planning. Three T_2 weighted (T2w) sequences were also applied, which included a 3D T2w steady state free precession [T2w fast field echo (T2-FFE)], and both 3D and two-dimensional T2w fast spin-echo (FSE) techniques [T2w volumetric isotropic T2w acquisition (T2-VISTA) and T2w turbo spin echo (T2-TSE)]. T_2 weighting yields inherently positive contrast of LNs but also requires a method for blood signal and fat suppression to provide endogenous high contrast with blood and fat. In the T2-VISTA technique, T_2 preparation with velocity encoding of 1 cm s^{-1} in caudal–cranial and right–left directions was applied by velocity-encoding preparation pulses, in order to eliminate signal from blood with a low flow velocity. The echo train lengths in T2-VISTA and T2-TSE were 65 and 33, respectively.

Finally, diffusion-weighted single-shot spin echo, echo planar imaging [diffusion-weighted imaging (DWI)] with four b -values (up to $b = 1000 \text{ s mm}^{-2}$) was performed. Signal preservation in DWI reflects motion restriction of water molecules. Water motion is more restricted in LNs than in background tissue and thus has higher signal intensity. A scan time of $<3 \text{ min}$ could be used for DWI, since resolution and signal-to-noise ratio (SNR) could not be improved by simply prolonging scan time. A known drawback of DWI is geometric distortions due to magnetic field susceptibility artefacts.²³ Hence, the geometric

Table 1. Imaging parameters of the optimized MRI scans. The field of view for each scan was 250, 420 and 100 mm in caudal–cranial (CC), right–left (RL) and anteroposterior directions, respectively

Sequences	T1-FFE	T2-FFE	T2-VISTA	T2-TSE	DWI
Imaging parameters					
TR/TE (ms)	5.7/1.9/3.8 ^a	12/4.8	155/2000	4500/100/2 ^b	6147/80
Fat suppression	mDixon	ProSet	SPAIR	mDixon	SPAIR
Dimensionality	3D	3D	3D	2D	2D
Acquired resolution	$1.0 \times 1.0 \times 2.2 \text{ mm}^3$	$0.7 \times 0.7 \times 2.0 \text{ mm}^3$	$1.0 \times 1.0 \times 2.0 \text{ mm}^3$	$0.7 \times 0.7 \text{ mm}^2$	$3.0 \times 3.0 \text{ mm}^2$
BW/pixel (Hz)	719	134	439	434	29
Slice thickness (mm)	–	–	–	3.0	3.0
Diffusion b -values (s mm^{-2})	–	–	–	–	0, 200, 400, 1000
Preparation/pre-pulse	–	–	$v_{\text{enc}} = 1.0 \text{ cm s}^{-1}$ (CC and RL)	–	–
Scan time (min:s)	3:06	6:30	3:24	4:50	2:15

2D, two dimensions; 3D, three dimensions; BW, bandwidth; DWI, diffusion-weighted imaging; mDixon, multipoint Dixon; ProSet, principle of selective excitation technique; SPAIR, spectral attenuated inversion recovery; T1-FFE, T_1 weighted fast field echo; T2-FFE, T_2 weighted fast field echo; T2-TSE, T_2 weighted turbo spin echo; T2-VISTA, T_2 weighted volumetric isotropic T_2 weighted acquisition; TE, echo time; TR, repetition time; v_{enc} , velocity encoding.

^aTR/TE1/TE2 (ms).

^bTR/TE/ Δ TE (ms).

reliability is limited, which can be determined by taking into account the pixel bandwidth and resolution (Table 1).

Fat suppression

On both T1w and T2w MRI, fat has high signal intensity. However, contrast between fat and LNs on T1w images is higher than on T2w scans. Since most LNs are located in or near fatty tissue, a method to suppress fat signal was applied in T2w MRI sequences. In the T1w sequence, a water–fat separation method was used because it was not obvious whether fat-suppressed images were beneficial.

One technique to suppress fat signal, applied in T2-VISTA and DWI, is spectral attenuated inversion recovery (SPAIR). In SPAIR, an adiabatic frequency-selective inversion pulse is used to invert the magnetization which originated from fat, followed by spoilers.^{24,25}

Another method is to separate water and fat. This was applied in the T1-FFE and T2-TSE scans, with mDixon. In this technique, multiple echoes are used to separate water and fat based on the phase and magnitude of the acquired signals. Therefore, it can provide both water-suppressed and fat-suppressed images.^{26,27}

The third method for fat-signal suppression, performed in T2-FFE, uses binomial water-selective pulses or principle of selective excitation technique consisting of a composite radio-frequency pulse with pre-defined flip angles and time intervals. The fat suppression is provided by exploiting the dephasing of fat and water.^{24,25}

Lymph node detection rates and statistics

As a quantitative evaluation of the MRI sequences, the numbers of right-sided axillary and supraclavicular LNs were determined in each scan for each volunteer. This was performed independently of the other MRI scans available for that volunteer. The scoring process was performed by one researcher who was extensively trained to identify regional LNs on MRI. During several interdisciplinary meetings, the researcher, together with a breast radiologist, breast radiation oncologist, MRI physicist and clinical physicist, assessed all MRI techniques and identified LNs. The team discussed regularly, in order to establish consensus on anatomical structure identification on the MRI sequences.

After the scoring process was completed, statistical analysis was performed by paired Wilcoxon signed-rank tests, between the LN detection rates in each MRI technique, for both LN areas. A significant difference is indicated by $p < 0.05$.

Imaging assessment

The MR images were assessed qualitatively by an experienced breast radiologist. For LN detection, maximum intensity projections of three slices were used to increase SNR and increase LN detection in T2-FFE and T2-VISTA. In both T1-FFE and T2-TSE, the water image of mDixon was used for evaluation. For evaluation of DWI scans, the highest diffusion weighting was chosen, *i.e.* $b = 1000 \text{ s mm}^{-2}$.

The following aspects were evaluated in view of suitability for LN delineation: contrast of the LNs to the surrounding tissue;

suppression of blood signal; fat suppression in the axillary and supraclavicular areas; visibility of anatomical reference structures, which is essential for localizing LNs; susceptibility to motion artefacts of the sequences; and SNR. The qualitative parameters were determined visually and given a score of “–” (very poor), “-” (poor), “±” (average), “+” (good), or “++” (excellent), on a five-point Likert scale.^{28,29}

RESULTS

Endurance for undergoing the MRI procedure was excellent in all volunteers. MRI of regional healthy LNs was achieved in the final 12 volunteers using the 5 optimized sequences (Figures 3 and 4). All numbers of right-sided LNs determined per volunteer and per scan are listed in Supplementary Table A and represented in Figure 5. The results of the qualitative evaluation are summarized in Table 2.

Quantitative evaluation

Of the five MRI techniques, the two T2w FSE techniques proved to have the highest LN detection rates (Figure 5). T2-VISTA showed the highest numbers in all 12 volunteers: up to 44 axillary (median: 24) and up to 5 supraclavicular LNs (median: 2) were detected. Statistical significances from the paired Wilcoxon signed-rank tests are indicated with respect to T2-VISTA in Figure 5.

T2-TSE showed similar numbers, at a median of 23 axillary and 2 supraclavicular LNs (ranges: 11–40 and 0–4, respectively). No difference was found between the two T2w FSE methods for either the axillary ($p = 0.47$) or supraclavicular ($p = 0.39$) LNs. The median number of axillary LNs identified with T1-FFE was 17, ranging between 10 and 21. This was higher than in T2-FFE (median 14, range: 9–19, $p = 0.01$). Moreover, T1-FFE showed a range of 0–4 supraclavicular LNs compared with the range of 0–2 found in T2-FFE, both showing a median number of one LN ($p = 0.05$). Finally, the number of LNs counted in the DWI scans was lowest in all subjects at a median of 10 axillary LNs. Moreover, in 10 out of 12 subjects, no supraclavicular LNs could be identified with the DWI technique, whereas only 1 supraclavicular LN was found in the other 2 volunteers. LN detection rate of DWI was by far the lowest of the 5 techniques ($p = 0.001$ axillary, $p = 0.002$ supraclavicular).

In the T2-VISTA and T2-TSE scans, the number of axillary LNs was significantly higher than for T1-FFE, T2-FFE and DWI ($p = 0.002$, 0.002 and 0.001 , respectively). This was also true for the supraclavicular LNs in T2-FFE and DWI ($p = 0.002$ for both) but not for T1-FFE ($p = 0.26$).

For 11 out of 12 individual subjects, T2-VISTA and T2-TSE showed a higher axillary LN detection rate than the T1-FFE, T2-FFE and DWI methods. For the other subject, T1-FFE and T2-TSE showed equal numbers of LNs, whereas T2-VISTA showed a lower number. This was due to degraded SNR and contrast in that particular T2-VISTA scan.

Qualitative evaluation

T1-FFE yielded excellent water–fat separation with mDixon, and the high resolution clearly showed individual LNs in the axilla and supraclavicular area. However, in the water image of

Figure 3. Coronal slices showing axillary lymph nodes (LNs) in five volunteers bilaterally, visualized with MRI. The MRI techniques represented are (a) T_1 weighted fast field echo (T1-FFE; water-only image); (b) T_2 weighted (T2w) volumetric isotropic T2w acquisition (T2-VISTA); (c) T2w turbo spin echo (T2-TSE; water-only image); and (d) T2w fast field echo (T2-FFE); and (e) diffusion-weighted imaging (DWI; $b = 1000 \text{ s mm}^{-2}$). For the T1-FFE, T2-VISTA and T2-FFE examples, maximum intensity projections of three slices were used to increase signal-to-noise ratio and to cover the same volume as in the T2-TSE and DWI.

mDixon, the signal of some LNs blended in with the surrounding soft tissue and blood vessels, thereby impeding identification of small structures. Anatomical landmarks, such as pectoral and deltoid muscles and arteries, were clearly visible

and could be used as structural references. The technique proved to be relatively insensitive to motion. Furthermore, the SNR was good (Table 2, Figures 3 and 4).

T2-FFE showed high contrast of the LNs in high resolution and excellent suppression of blood due to intrinsic diffusion weighting, but the water-selective binomial pulses resulted in poor fat suppression in the supraclavicular region (Figure 3). Furthermore, some LNs located near pulsating arteries were obscured due to motion (Figure 4). Obscuration of LNs was also observed after gross motion of the volunteer during scanning. The latter was evident in two volunteers. The high susceptibility to motion artefacts affects T2-FFE to a large extent. Moreover, the SNR in T2-FFE was relatively low (Table 2).

Both FSE techniques showed high T_2 contrast of the LNs, with successful fat suppression in the axilla. In the supraclavicular area, fat was excellently suppressed by mDixon in the water-only image of T2-TSE, but SPAIR fat suppression in T2-VISTA failed in four cases. The regional LNs could clearly be identified in both FSE scans, and even minute LNs were detectable. However, both FSE sequences still showed some remaining blood signal. Additionally, T2-VISTA showed slightly more blurring than T2-TSE. In the latter, anatomical reference structures, such as the pectoral and deltoid muscles, were better visible than in the T2-VISTA scans. Both T2w FSE sequences were robust for motion. SNR of the FSE images was average and good for T2-VISTA and T2-TSE, respectively (Table 2, Figures 3 and 4). In one case, however, T2-VISTA was greatly outperformed by T2-TSE in terms of LNs contrast and SNR.

Finally, DWI yielded high LN contrast relative to all surrounding tissue, but it has an inherently low resolution. Furthermore, no anatomical reference structures were clearly visible in DWI due to very efficient background suppression. The technique proved to be very insensitive to motion during acquisition. Nevertheless, DWI yielded low SNR (Table 2, Figures 3 and 4). Furthermore, visual inspection suggested geometric inaccuracies due to the high sensitivity to magnetic-field variations, which led to pixel shifts of up to 15 mm. Analogously to T2-VISTA, SPAIR fat suppression in DWI worked successfully in the axillary region but failed in four cases in the supraclavicular area.

DISCUSSION

As a first step towards MRI-guided regional breast RT, this study explored MRI for visualizing healthy LNs in supine RT position. 5 clinically applicable MRI sequences were optimized in 10 female healthy volunteers and subsequently evaluated in another 12 female healthy volunteers. Evaluation of the MRI methods was aimed at the potential suitability for LN delineation in RT planning.

Although MRI for axillary LN imaging is thoroughly studied,³⁰ MRI studies for target delineation in regional breast RT are scarce. Diagnostic MRI is performed for staging of the tumour and/or regional LNs, and scans are usually acquired in prone position. These techniques include contrast-enhanced T1w MRI methods, as well as T2w sequences and DWI.^{22,31} LN staging is usually based on size of LNs, relative T_2 values, morphology,

Figure 4. Coronal slices showing right-sided axillary lymph nodes (LNs) in one volunteer, visualized with MRI. The slices shown are cropped to approximately $80 \times 80 \text{ mm}^2$. Location with respect to anatomy is depicted schematically by the square in (a). MRI techniques represented are (b) T_1 weighted fast field echo (T1-FFE; water-only image); (c) T_2 weighted (T2w) volumetric isotropic T2w acquisition (T2-VISTA); (d) T2w turbo spin echo (T2-TSE; water-only image); (e) T2-FFE; and (f) diffusion-weighted imaging (DWI; $b = 1000 \text{ s mm}^{-2}$). For the T2-VISTA and T2-FFE examples, maximum intensity projections of three slices were used to increase signal-to-noise ratio and to cover the same volume as in the T2-TSE and DWI. The arrows indicate LNs, apparent in T1-FFE, T2-VISTA, DWI and T2-TSE but obscured in T2-FFE due to a pulsating artery nearby. The arrowheads indicate a LN that is clearly identifiable in the T2w and DWI sequences but lacks contrast in T1-FFE. ax. a. v., axillary artery and vein; m. lat. d., musculus latissimus dorsi.

contrast agent uptake or a combination of these.¹⁹ Recently, DWI has become popular due to the high signal intensity of LNs relative to surrounding tissue.^{32,33} Furthermore, apparent diffusion coefficients can be calculated from DWI for an indication for malignancy. In contrast to these diagnostic methods, the MRI techniques presented here are acquired in supine RT position, without administration of contrast agent, using anterior and posterior receive coils. They were specifically optimized to image regional LNs explicitly for RT planning.

Two FSE techniques, T2-VISTA and T2-TSE, showed the highest LN detection rates while being relatively insensitive to motion during acquisition. Both sequences have specific advantages and limitations. Contrast of LNs relative to the background is high in

both techniques due to successful fat suppression such that individual LNs could be directly identified. The techniques differ in resolution as the T2-TSE is a multislice method with 3-mm slices, which might be a disadvantage for accuracy in target delineation. T2-VISTA has 1-mm isotropic resolution but showed some blurring due to a long echo train. Although both sequences were optimized to show black blood, some signal remained visible in axillary blood vessels. Additional T_2 weighting induced by the preparation pulses for velocity encoding caused loss of background signal. In one volunteer, this degraded SNR and LN contrast severely in the T2-VISTA.

T1-FFE showed fewer LNs, as contrast between LNs and blood vessels or muscles is lacking, due to the limited T_1 differences

Figure 5. Numbers of lymph nodes (LNs) identified in images acquired with different MR sequences. For both (a) the axilla and (b) the supraclavicular area, the numbers of detected LNs are denoted, per MRI technique, for all 12 volunteers. Note that the y-axes in (a) and (b) differ. T_1 weighted fast field echo (T1-FFE) is denoted by dots, T_2 weighted (T2w) fast field echo (T2-FFE) by squares, T2w volumetric isotropic T2w acquisition (T2-VISTA) by triangles pointing upwards, T2w turbo spin echo (T2-TSE) by triangles pointing downwards and diffusion-weighted imaging (DWI) by black diamonds. Black horizontal lines indicate the median values. Statistical significances from paired Wilcoxon signed-rank tests are indicated with respect to T2-VISTA. * $p < 0.05$; n.s., non-significance or $p > 0.05$.

between these tissues. Consequently, LNs could be unnoticed or other structures could be misidentified to be LNs. This issue could be addressed by including water-fat images provided by mDixon. A fatty core might help to differentiate a LN from other tissues. The presence of anatomical information makes the robust T1-FFE sequence valuable for RT planning and complementary to the T2w FSE techniques. Furthermore, T2-FFE

proved to be unsuitable since LNs are obscured due to motion. Finally, DWI while robust for motion artefacts due to rapid image acquisition and showing high LN contrast at high b -values suffered from geometric inaccuracies and low resolution, which is inherent to echo planar imaging-based sequences.

Since most regional LNs are located in or near fatty tissue, a method for suppression of fat signal was applied. Fat-suppression techniques can be adversely affected by B_0 inhomogeneities. These are found particularly in the supraclavicular area, due to ubiquitous tissue-air transitions and sharp curvature of the outer contour. In our study, mDixon proved to be very reliable—even in subjects with a high BMI (up to 31.2 kg m^{-2}). The mDixon method is relatively insensitive to B_0 irregularities,^{26,27,34} but the use of multiple echoes requires a longer scan duration. Conversely, the water-selective binomial pulse principle of selective excitation technique performed poorly due to B_0 non-uniformities. SPAIR, as frequency-selective inversion pulse, was only slightly impaired.

The gold standard for the total number of LNs is not available. Therefore, the key question is how accurate the MRI sequence of choice is. In previous imaging (including MRI, CT and ultrasonography) and histological studies,^{35–42} numbers of axillary LNs, both benign and malignant, ranged between 6 and 45, emphasizing large (anatomical) variation between subjects. In these studies, the goal was to compare diagnostic values of imaging techniques in correlation with histology, rather than establish LN detection capability. Histological information, usually after ALND, is limited to the lower axilla (*i.e.* axillary levels I and II), whereas our work aimed to image LNs in the entire regional area (*i.e.* axillary levels I, II and III and supraclavicular region). Numbers of axillary LNs detected with the MRI sequences in our work fall in the reported range. Finally, numbers of LNs observed in the supraclavicular region were within the expected range of 1–10 LNs.⁴⁰ This region is particularly difficult, due to large pulsating blood vessels which were not always adequately suppressed in the FSE scans, thereby possibly impairing localization of small LNs there.

This study showed the technical feasibility of explicitly visualizing healthy LNs using MRI in volunteers. Furthermore, endurance to undergo the entire MRI procedure was excellent. Quantitative and qualitative analyses indicated that MRI and, in particular, the T2w FSE and T1-FFE sequences could be excellent tools for explicit LN delineation. In order to assess the added value of these methods for RT planning, the next step will be MRI in patients with breast cancer. In our study, a large range of BMI was chosen ($19.4\text{--}31.2 \text{ kg m}^{-2}$) to reflect the expected patient population, but several issues remain to be investigated. Endurance and anatomy in patients are likely to differ from those in the healthy volunteers. LN morphology could also change with age.^{43,44} Moreover, any axillary surgery (*e.g.* sentinel-node biopsy) might affect LN detection rates in MRI. These aspects, as well as image quality and patient set-up reproducibility,⁴⁵ are under investigation in a patient study that is ongoing at UMC Utrecht. Patient data will also allow a comparison of MRI and CT scans, both in supine RT position.

Table 2. Qualitative evaluation of the MRI sequences. Results from scans in healthy female volunteers ($n = 12$) determined visually. Classifications on a five-point Likert scale: “++” = excellent; “+” = good; “±” = average; “-” = poor; “--” = very poor. In T_1 weighted fast field echo (T1-FFE) and T_2 weighted (T2w) turbo spin echo (T2-TSE), multipoint Dixon (mDixon) was applied, whereas in T2w fast field echo (T2-FFE), principle of selective excitation technique was used for fat suppression. In T2w volumetric isotropic T2w acquisition (T2-VISTA) and diffusion-weighted imaging (DWI), fat was suppressed by spectral attenuated inversion recovery. For this evaluation, only the water image from the mDixon method was taken into account. The highest diffusion weighting ($b = 1000 \text{ s mm}^{-2}$) was used for evaluation of DWI

Sequence	T1-FFE	T2-FFE	T2-VISTA	T2-TSE	DWI
Qualitative parameters					
Contrast of LNs	-	+	+	+	++
Axillary fat suppression	++	+	+	++	+
Supraclavicular fat suppression	++	-	+	++	±
Blood suppression	NA	++	+	+	++
Visibility of anatomical reference structures	++	±	±	+	--
Insusceptibility to motion artefacts	++	--	+	+	-
SNR	+	-	±	+	±

LNs, lymph nodes; NA, not applicable; SNR, signal-to-noise ratio.

The MRI techniques presented potentially have a high added value for clinical practice. Localizing individual LNs may lead to adaptation of standard target volumes,³⁶ as currently defined on CT. A possible consequence of MRI guidance is smaller treatment fields and, thus, reduced treated volume. This may result in a lower integral dose, organs-at-risk sparing and, thereby, a reduction of RT-induced toxicity. Furthermore, combining RT with dedicated MRI could enable more selective regional RT. However, in the current clinical situation, due to set-up uncertainties of regional RT, introducing these new RT techniques requires LN visualization while the patient is treated. On-line MRI guidance could achieve this, as enabled by the UMC Utrecht MRI/linear accelerator.⁴⁶ Relative to current treatment techniques, the MRI/linear accelerator and other MRI/RT modalities^{47,48} could allow for personalized treatments, such as stereotactic RT of individual tumour-positive LNs. For such

advanced RT techniques, methods for identifying metastatic LNs on MRI, with a high sensitivity, could be beneficial.¹⁹ Ultimately, patients with breast cancer may benefit from the many possibilities of MRI of the regional LNs.

CONCLUSION

Identification of individual axillary and supraclavicular LNs is feasible with MRI in supine RT position. Two T2w FSE techniques were robust and showed the highest numbers of LNs, whereas a T1-FFE method provided the most anatomical information. Fat separation by mDixon performed excellently. This work serves as a required first step to investigate MRI guidance in regional RT for patients with breast cancer. By identifying individual LNs, MRI-based target delineation could reduce target volumes and thereby further reduce RT-induced toxicity in the future.

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