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Original Article

A Prospective Study of Magnetic Resonance Imaging Assessment of Post-radiation Changes Following Stereotactic Body Radiation Therapy for Non-small Cell Lung Cancer

P. Munoz-Schuffenegger *†, S. Kandel ‡, Z. Alibhai *†§, A. Hope *†, A. Bezjak *†, A. Sun *†, A. Simeonov *†, B.C.J. Cho *†, M. Giuliani *†

* *Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto, Ontario, Canada*
† *Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada*
‡ *Joint Department of Medical Imaging, University of Toronto, Toronto, Ontario, Canada*
§ *Department of Radiation Oncology, Southlake Regional Cancer Centre, Newmarket, Ontario, Canada*

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Abstract

Aims: Follow-up computed tomography scans after lung stereotactic body radiation therapy (SBRT) are difficult to interpret due to the presence of benign fibrosis, which can make the detection of local recurrence difficult. The objective of this study was to determine the feasibility of a novel thoracic magnetic resonance imaging (MRI) protocol incorporating diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) imaging for the assessment of the treated lung parenchyma after SBRT.

Materials and methods: On a prospective trial, post-treatment MR images were acquired in 30 patients treated with SBRT (divided into three different cohorts according to the likelihood of local recurrence as per an expert panel). These images were assessed by an expert thoracic radiologist blind to clinical data, who indicated local recurrence in a dichotomous manner. Local recurrence was confirmed by biopsy or subsequent growth on follow-up computed tomography scans.

Results: Thirty patients underwent MRI as part of this study; 27/30 patients were analysable for local recurrence. MRI was conducted at a median of 27.3 months (range 6.5–71 months) from SBRT. No side-effects resulted from either MRI or contrast administration. At a median follow-up time of 45 months after treatment, three local recurrence episodes have occurred. MRI assessment diagnosed seven patients as having a local recurrence, which was later confirmed in three and did not miss any of the true local recurrences. When comparing apparent diffusion coefficient (ADC) values according to local recurrence, the mean ADC value for the local recurrence-free group was 1770×10^{-3} mm/s^2 (range $1038–3105 \times 10^{-3}$ mm/s^2) versus 981×10^{-3} mm/s^2 (range $926.6–1065 \times 10^{-3}$ mm/s^2) for the local recurrence group ($P = 0.0014$).

Conclusions: A novel 3.0 T MRI protocol incorporating DWI and DCE was feasible and confirmed the suspicion of local recurrence in patients with highly suspicious computed tomography scans. This imaging tool could potentially aid in selecting patients for salvage treatment after local SBRT failure. Future work should be pursued to validate these findings.

Key words: Early stage non-small cell lung cancer; local recurrence; magnetic resonance; stereotactic body radiation therapy

Introduction

Stereotactic body radiation therapy (SBRT) has emerged as a standard of care for the treatment of early stage non-small cell lung cancer (NSCLC) in patients who are medically inoperable or refuse surgical resection [1,2]; it achieves local control rates of 90% at 3 years after treatment [3] comparable with those of surgery. Local recurrences, although infrequent, usually manifest at a median time of 15 months after SBRT [4] and successful surgical or non-surgical salvage can be carried out with curative intent in selected patients [5–7].

Benign fibrotic changes arising on follow-up computed tomography scans after SBRT are difficult to interpret and reliably differentiate from local recurrence [8]. At least two post-SBRT

Author for correspondence: M. Giuliani, Radiation Medicine Program, Princess Margaret Cancer Centre, 610 University Ave, Toronto, ON, M5G 2M9, Canada. Tel: +1-416-946-2983; Fax: +1-416-964-6561.
E-mail address: Meredith.Giuliani@rmp.uhn.ca (M. Giuliani).

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fibrosis categorisation systems have been described in the literature [9,10], but given the dynamic nature of radiation-induced lung fibrosis, and its considerable inter-rater variability [11], there is still the need to further characterise fibrotic changes and accurately predict local recurrence [12]. Furthermore, more than 50% of patients develop at least one of these 'high-risk features' on follow-up computed tomography scans [13], emphasising the need to study and develop accurate methods for local recurrence prediction and diagnosis.

Magnetic resonance imaging (MRI) is a diagnostic tool that provides better soft-tissue imaging than computed tomography scans. The use of thoracic MRI was previously limited due to motion artefacts related to breathing and vascular pulsation, but recent advances in MRI technology have addressed these issues [14,15]. MRI provides not only morphological but also functional information, with diffusion-weighted and perfusion sequences providing quantitative and qualitative information about the integrity of cell membranes and tissue consistency, which reflect changes at a cellular level that could be useful in separating local recurrence from radiation-induced lung fibrosis.

The purpose of this study was to determine the feasibility of thoracic MRI, incorporating diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) analysis, to assess treated lung parenchyma for recurrence after SBRT for early stage NSCLC.

Materials and Methods

This prospective clinical trial was approved by the institutional ethics committee and was carried out in accordance with the guidelines of the Helsinki declaration. Written informed consent was obtained from all subjects. This study was registered with the U.S. National Institutes of Health (NCT01480937).

Patients

The study population consisted of patients with early stage (T1, T2, N0) NSCLC (according to the seventh edition of the American Joint Committee on Cancer Staging Manual) who were treated with SBRT as per institutional guidelines. The patients received one of three dose regimens: 48 Gy in four fractions (12 Gy per fraction delivered every other day) for peripheral tumours < 3 cm; 54 Gy in three fractions (18 Gy per fraction delivered every other day) for peripheral tumours > 3 cm; or 60 Gy in eight fractions (7.5 Gy per fraction delivered once per day) for central tumours. All patients were followed up per protocol at 6 weeks after SBRT with a chest X-ray, then computed tomography of the thorax at 3, 6, 9, 12, 18 and 24 months, and annually thereafter. Computed tomography of the thorax was carried out more frequently if there were clinical indications for more frequent imaging.

Patients whose follow-up computed tomography of the thorax showed radiological changes in the previously treated lung parenchyma suggestive of fibrosis, equivocal or suspicious of recurrence at any time were approached to participate in this study. At the time of enrolment, previous treatment plans and follow-up computed tomography scans were discussed in our Lung Radiation Oncology Quality Assurance Rounds. As a group consensus, patients were assigned into one of three cohorts according to the radiological features of their treated lung parenchyma: felt to be related to fibrosis (cohort 1: $n = 10$), changes that were equivocal (cohort 2: $n = 10$) and patients whose changes were suspicious for recurrence (cohort 3: $n = 10$). To include a representative spectrum of radiological changes in the lung parenchyma after SBRT, this study aimed to enrol 30 patients, divided into three different cohorts of 10 patients each. As part of this study, patients underwent MRI of the thorax as detailed below.

Exclusion criteria for this study were any contraindication to MRI, including the presence of metallic foreign bodies or prosthesis, gadolinium contrast agent allergy or known claustrophobia. Patients who underwent lung surgical resection in the same area of SBRT after radiation treatment were also excluded from this study.

On subsequent follow-up computed tomography scans, suspicion of local recurrence was confirmed with a biopsy whenever possible. In those cases where a biopsy was not feasible or the patient declined to have a biopsy, local recurrence was defined as consistent growth on three consecutive computed tomography scans carried out at least 2 months apart from each other.

Magnetic Resonance Imaging Acquisition

Multiparametric MRI was carried out on a Siemens 3.0T MAGNETOM® Verio System, body matrix 8 channel coil and including sequences such as Half Fourier Acquisition with Single Shot Turbo Spin Echo (HASTE), Prospective Acquisition CorrEction (PACE), DWI and DCE imaging (see Appendix A for details).

If significant artefacts were presented in the MRI data, due to distortion or patient motion, they were excluded from the analysis.

All MRI data were transferred to a PACS workstation for post-processing and analysis. Apparent diffusion coefficient (ADC) values were calculated automatically and displayed as parametric maps. An experienced thoracic radiologist (SK), blind to the clinical data and the pre-stratified risk group classification by the broader group, carried out ADC measurements within the lung parenchymal changes and paraspinal muscles by drawing regions of interests on the ADC maps. DCE images were analysed qualitatively and a dichotomous decision regarding recurrence (yes or no) was made at the time of this evaluation (by SK). Notably, local recurrences either showed fast enhancement within the first minute after the administration of intravenous contrast material with slow washout and late enhancement of fibrosis or there was an inhomogeneous enhancement of post-radiation changes with a more focal area of increased enhancement in comparison with the surrounding fibrotic tissue.

Statistical Analysis

Patient characteristics were described as proportions and means. Local recurrence-free survival, progression-free

survival and overall survival were calculated using the Kaplan–Meier method. ADC values between treatment groups were compared using a one-way ANOVA test and an exploratory comparison between patients who experienced local recurrence and those who did not was carried out using the Mann–Whitney U test. The results were analysed by the use of the IBM SPSS package (IBM Corporation) version 24; P values < 0.05 were considered statistically significant.

Results

Patients' Baseline Characteristics

Between July 2011 and January 2017, 30 patients were accrued into this study. The baseline characteristics for these 30 patients are described in Table 1. The median age at diagnosis was 70.5 years (range 44–87 years). Nineteen patients (63%) were men. Eight patients (26.7%) had previous lung surgery for stage I NSCLC; six patients (20%) had previous SBRT for stage I NSCLC. Regarding their radiation treatment, the median dose to the planning target volume was 48 Gy (range 48–60 Gy) and the median number of fractions was four (range three to eight). Five patients did not have biopsy confirmation due to being unfit for a biopsy.

Progression-free and Overall Survival

The median follow-up time from the completion of SBRT was 45 months (range 6–104 months). At the time of this analysis, 11 patients had experienced disease progression, either local, regional or distant; the median progression-free survival was 68 months (range 53.0–82.92 months). The 5-year overall survival for this treatment population was 58%.

Table 1
Patient characteristics

	($n = 30$)
Age, years, median (range)	71 (44–87)
Tumour size, mm, mean (standard deviation)	20.1 (10.1)
Male (%)	63%
Involved lobe	
RUL	10
RML	1
RLL	9
LUL	8
LLL	2
Previous lung surgery	6
Previous lung radiotherapy	7
Histology	
Adenocarcinoma	15
Squamous cell	7
NSCLC	3
No pathological diagnosis	5
SBRT schedule	
54 Gy in 3 fractions	2
48 Gy in 4 fractions	24
60 Gy in 8 fractions	4

LLL, left lower lobe; LUL, left upper lobe; NSCLC, non-small cell lung cancer; RLL, right lower lobe; RML, right mid-lobe; RUL, right upper lobe; SBRT, stereotactic body radiation therapy.

Magnetic Resonance Imaging

Thirty patients underwent MRI per study protocol. However, three patients were subsequently excluded from the analysis due to imaging artefacts or other limitations. In one patient, the target lesion was not adequately covered during the DWI sequences; in another patient, the apical portion of the treated lesion was not adequately imaged. In a third patient the lesion was too small for an adequate DWI analysis. These lesions were located in the right upper lobe, right lower lobe and left lower lobe, respectively.

The median time between the last SBRT fraction and MRI was 27.3 months (range 6.5–71 months). The duration of each MRI study was about 50–60 min per patient. No side-effects from either the imaging procedure or the MRI contrast were reported during or after MRI.

Local Recurrences: Clinical and Magnetic Resonance Imaging Assessment

The MRI assessment, including morphological as well as DWI and DCE datasets, was conducted in 27 patients. Overall, seven patients were diagnosed as having a local recurrence as per MRI; three were later confirmed in concordance with clinical outcomes (two of these three recurrences were biopsy proven). MRI did not diagnose any patients with clinical local recurrence as disease free.

In cohort 1 (fibrosis), MRI assessment conducted 21 months after SBRT diagnosed one patient as having a local recurrence; this was not confirmed on subsequent computed tomography scans. This patient developed distant failure 3 years after treatment and died 4 months later without signs of local recurrence on follow-up computed tomography scans (Figure 1) (Figure 2).

In cohort 2 (equivocal for recurrence), MRI assessments diagnosed two of eight patients as having a local recurrence; one of these was confirmed on follow-up. For the patient with a local recurrence, MRI was carried out 23

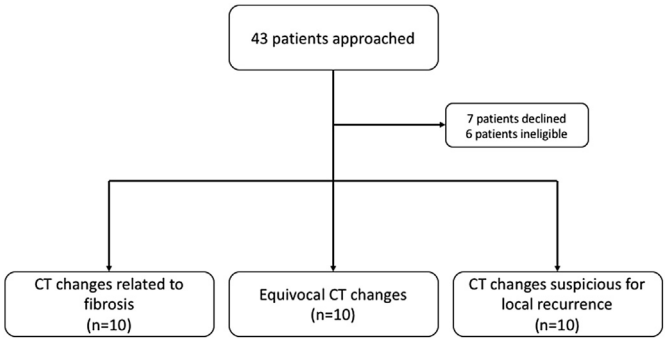

Fig 1. Study population flowchart.

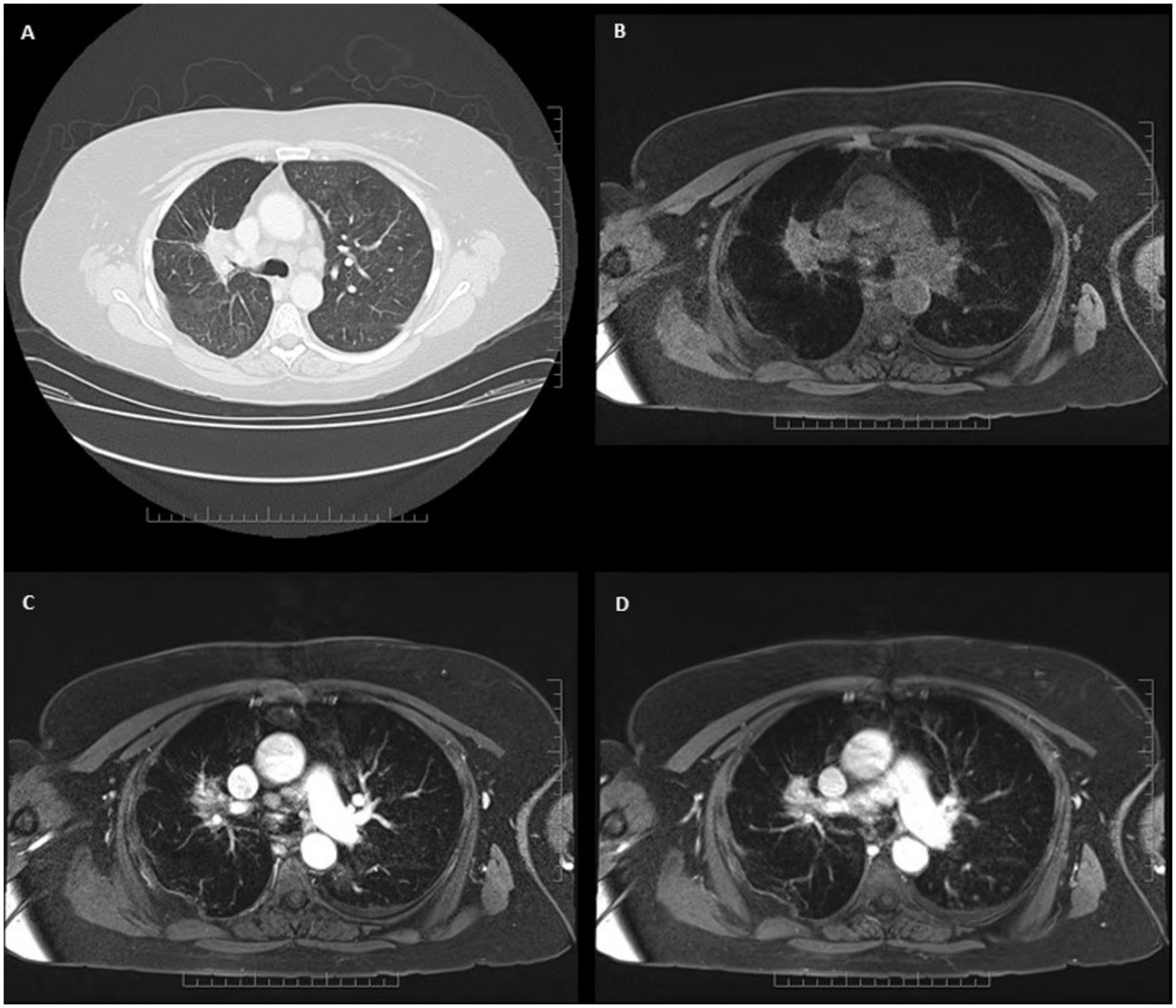

Fig 2. Example of a patient with a follow-up computed tomography scan scored as equivocal for recurrence (A). (B) 3.0T T1 sequence before contrast administration. (C) and (D) Dynamic contrast-enhanced assessment at 20 s and 1 min after contrast administration. A magnetic resonance imaging assessment diagnosed these findings as benign, which was later confirmed on subsequent follow-up.

months after SBRT; subsequent follow-up computed tomography scans showed consistent growth, confirming a local recurrence 8 months later. For the patient without recurrence, MRI was carried out 29 months after SBRT; this patient remains disease free 4.5 years after treatment.

In cohort 3 (suspicious for recurrence according to computed tomography scan), MRI assessment diagnosed four of nine patients as having a local recurrence; one was confirmed with a fine needle biopsy; a second was confirmed by consistent growth on subsequent computed tomography scans. The first patient had the study MRI 28 months after treatment, when his computed tomography scan showed images highly suspicious of local recurrence; he then had a confirmatory fine needle biopsy. The second patient had the study MRI 12 months after SBRT, at the same time that a second follow-up computed tomography scan showed consistent tumour growth. The other two patients diagnosed as having local recurrence on MRI remained free of local recurrence until their last follow-up: the first patient developed distant failure at 23 months after treatment and died due to disease progression 24 months later. The second patient died of other causes 57 months after treatment, remaining disease free after his treatment (Figure 3).

Table 2 Summarises MRI findings and compares them with the clinical course of this patient population.

ADC Calculation and Analysis

An ADC calculation was carried out in 27 MRI datasets as previously discussed .

The mean ADC values for cohorts 1, 2 and 3 were 1827.2×10^{-3} mm/s^2 (range $1038–3105 \times 10^{-3}$ mm/s^2), 1821×10^{-3} mm/s^2 (range $926.6–2945 \times 10^{-3}$ mm/s^2) and 1783×10^{-3} mm/s^2 (range $981–2363 \times 10^{-3}$ mm/s^2), respectively. When these ADC values were compared, these differences were not statistically significant (cohort 1 versus cohort 2: $P = 0.9849$; cohort 1 versus cohort 3: $P = 0.8730$).

Table 2
Recurrences according to magnetic resonance imaging assessment and comparison with clinical outcomes

		Local recurrence (biopsy proven or consistent growth on computed tomography scans)					
		Fibrosis		Equivocal		Suspicious	
		Yes	No	Yes	No	Yes	No
Magnetic resonance imaging	Yes	0	1	1	2	2	2
	No	0	9	0	6	0	5

In an exploratory analysis, ADC values from patients with either clinical ($n = 2$) or pathologically proven ($n = 1$) local recurrence were compared with those of patients without local recurrence ($n = 24$). The mean ADC value for the recurrence-free group was 1770×10^{-3} mm/s^2 (range $1038–3105 \times 10^{-3}$ mm/s^2) versus 981×10^{-3} mm/s^2 (range $926.6–1065 \times 10^{-3}$ mm/s^2) for the recurrence group ($P = 0.0014$) (Figure 4).

Discussion

Surveillance after lung SBRT remains a challenge, as radiation-induced lung fibrosis can mimic local recurrence, leading in some cases to invasive diagnostic procedures where resection of lesions ultimately proved only to contain fibrotic tissue [7,16]. With a shift towards the use of SBRT for patients declining surgery, or borderline operative candidates, modern cohorts of patients treated with SBRT are fit and are expected to have longer life expectancies and, as such, are expected to be suitable candidates for surgical or non-surgical salvage treatment [7,17,18].

Previous studies have described qualitative high-risk computed tomography features that can potentially discriminate between SBRT-induced fibrosis and tumour recurrence [19]. Recently, Ronden *et al.* [13], analysing a cohort of 432 patients treated with SBRT for early stage NSCLC, reported the presence of high-risk features in more than 50% of patients

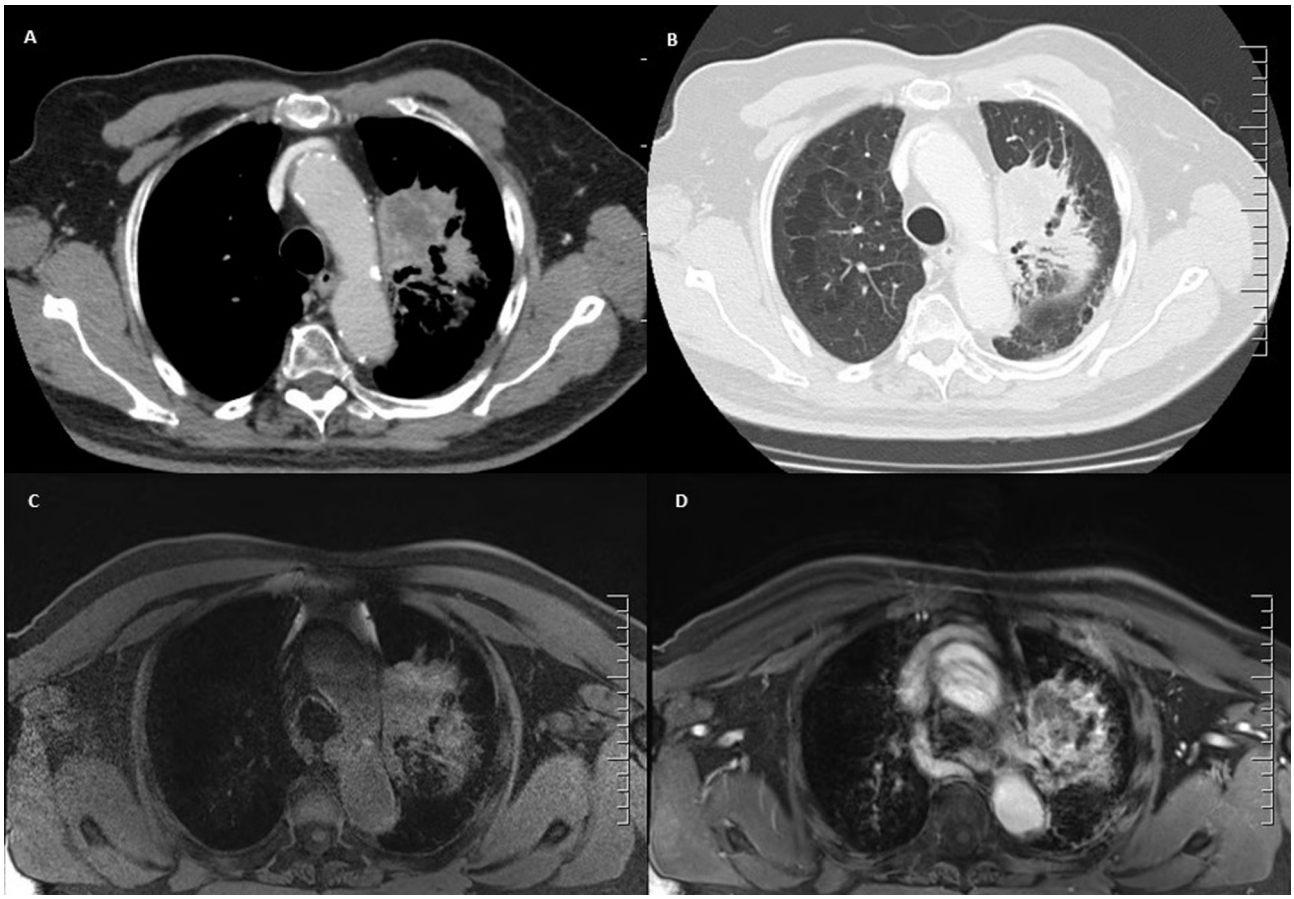

Fig 3. Example of a patient with a follow-up computed tomography scan scored as highly suspicious for recurrence (A, B). (C) 3.0T T1 sequence before contrast administration. (D) Dynamic contrast-enhanced assessment at 20 s after contrast administration. Magnetic resonance imaging assessment diagnosed these findings as recurrence, which was later confirmed on subsequent follow-up.

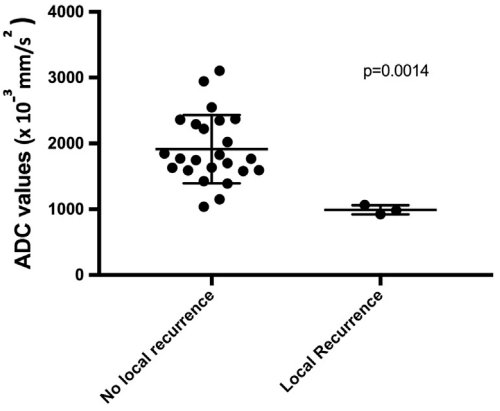

Fig 4. Scatter plot comparing apparent diffusion coefficient (ADC) values from patients with local recurrence with those from patients without local recurrence. The mean and standard deviation are plotted for each group.

without a local recurrence on long-term follow-up, together with a considerable interobserver variability at the time of scoring. This further emphasises the need to refine further the diagnosis of local recurrence on follow-up.

By extracting quantitative information from conventional computed tomography scans, radiomics has been studied as a potential tool to enhance local recurrence detection. Mattonen *et al.* [20] conducted a study analysing 182 computed tomography scans from 45 patients. Among a group of dedicated thoracic radiation oncologists, there was only moderate interobserver agreement and a median time to detection of recurrence of 15.5 months. When determining the early prediction of local recurrence within 6 months after SBRT, a radiomic signature outperformed physician assessment regarding classification error, false-positive and false-negative rates [20]. This work is pending validation and could potentially increase local recurrence detection on computed tomography scans.

MRI has previously been used to assess the treatment response to SBRT in early stage NSCLC. Iizuka *et al.* [21] conducted a preliminary study in 15 patients in which a combination of 1.5T DW MRI and FDG positron emission tomography (PET) was used to predict disease progression after SBRT for early stage NSCLC. In this cohort, a combination of a low pre-treatment ADC value and a high SUV_{max} was associated with an increased risk of disease recurrence. The same group recently published an update of this study [22], in which an exploratory analysis revealed that, at 3 and 6 months, the median ADC value was significantly lower in patients with local recurrence compared with those without local recurrence. Our study, on the other hand, used a 3.0T MRI unit; intraindividual comparison of imaging lung pathology at 1.5T and 3T has not been carried out in more extensive studies. Based on the three key critical drivers on image quality (scan time, signal to noise ratio and susceptibility artefacts) there are no substantial quality differences in the lung [23,24]. It has been shown that 1.5T and 3T are similar with regards to sensitivity and specificity to differentiate between malignant and benign pulmonary nodules [25]. Our study used HASTE, PACE and DW sequences, and also added DCE sequences, which were not used in the previous study assessing the treatment response after SBRT; finally, our findings regarding ADC values, although exploratory, are consistent with the observation by Iizuka *et al.* [21].

In our study, all 30 patients completed the study imaging and 27 datasets were analysable. There was a considerable time range from completing SBRT to the study MRI, as the study aimed to supplement the recurrence diagnosis, which can happen at any point. Interestingly, MRI was concordant with the three clinical recurrences diagnosed during the study and did not miss any of these. Moreover, in 10 patients who were highly suspicious of having a local recurrence, MRI narrowed down this initial assessment to four patients and two of them were finally confirmed to have a recurrence; only one had a pathologically confirmed local recurrence. However, it still misdiagnosed four patients as having a local recurrence, particularly in those groups with a lower likelihood of having one according to their assigned cohort.

To the best of our knowledge, this is the largest study that has been conducted on MRI assessment of parenchymal lung changes after SBRT. This patient cohort is representative of the array of parenchymal changes that are seen after lung SBRT for early stage NSCLC. It also included patients who, according to their follow-up computed tomography scans, represented different pre-test probabilities for local recurrence according to an expert radiation oncology team. All MR images were conducted at the same institution and in the same MRI machine, and images were analysed by the same radiology expert, which supports the consistency of this diagnostic intervention and analysis.

There are limitations to this study. During the study accrual period, 17 patients who were approached for the study were ultimately not eligible or declined to participate. As the patient population who received lung SBRT is often older adults, many with medical comorbidities, issues such as renal function and the presence of pacemakers or other metal devices can limit the use of MRI scans in this patient population. As only one experienced thoracic radiologist was involved in this study, replicating these results outside the context of a highly specialised radiology department could be challenging. The small number of patients with confirmed local recurrence makes it difficult to make definite conclusions regarding MRI morphological and functional characteristics of local recurrences diagnosed on MRI and later confirmed. Also, from three patients with local recurrences, only one had pathological confirmation, as sometimes this is not possible due to comorbidities, or may not be pursued if there are no other treatment options. MRI has technical limitations, and three patients had to be excluded from functional MRI assessments as their lesions were not adequately imaged.

Future work on MRI assessment will focus on validating these findings in a larger cohort, defining ADC threshold values for predicting local recurrence, as well as the expansion of this concept to PET/MRI platforms that can potentially provide quantitatively accurate multiparametric datasets consisting of molecular information from both PET and MRI [26]. Guidelines have recently been published on

the imaging modality and interval for follow-up after lung SBRT for early stage NSCLC, supporting the ancillary role of computed tomography on follow-up imaging [27]. Given the high costs of thoracic MRI, a potential role for thoracic MRI on follow-up would probably only be in the context of a high suspicion of recurrence based on computed tomography images.

In conclusion, MRI incorporating qualitative and quantitative assessment by an experienced thoracic radiologist was feasible and diagnosed local recurrence in three patients in which this was later confirmed, without missing any local recurrence episodes. This imaging tool has the potential to refine the diagnosis of local recurrence after lung SBRT, which could lead to a better selection of patients for radical treatment and fewer unnecessary invasive diagnostic procedures in patients who only have benign lung injury after lung SBRT.

Conflict of Interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.05.014.

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