

Volume assessment magnetic resonance imaging technique for monitoring perianal Crohn's fistulas

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Abstract

Background: Perianal Crohn's fistula and their response to anti-tumour necrosis factor (TNF) therapies are best assessed with magnetic resonance imaging (MRI), but radiologist reporting is subjective and variable. This study investigates whether segmentation software could provide precise and reproducible objective measurements of fistula volume.

Methods: Retrospective analysis of patients with perianal Crohn's fistula at our institution between 2007 and 2013. Pre- and post-biologic MRI scans were used with varying time intervals. A total of two radiologists recorded fistula volumes, mean signal intensity and time taken to measure fistula volumes using validated Open Source segmentation software. A total of three radiologists assessed fistula response to treatment (improved, worse or unchanged) by comparing MRI scans.

Results: A total of 18 cases were reviewed for this pilot study. Inter-observer variability was very good for volume and mean signal intensity; intra-class correlation (ICC) 0.95 [95% confidence interval (CI) 0.91–0.98] and 0.95 [95% CI 0.90–0.97] respectively. Intra-observer variability was very good for volume and mean signal intensity; ICC 0.99 [95% CI 0.97–0.99] and 0.98 [95% CI 0.95–0.99] respectively. Average time taken to measure fistula volume was 202 s and 250 s for readers 1 and 2. Agreement between three specialist radiologists was good [κ 0.69 [95% CI 0.49–0.90]] for the subjective assessment of fistula response. Significant association was found between objective percentage volume change and subjective consensus agreement of response ($p = 0.001$). Median volume change for improved, stable or worsening fistula response was –67% [interquartile range (IQR): –78, –47], 0% [IQR: –16, +17], and +487% [IQR: +217, +559] respectively.

Conclusion: Quantification of fistula volumes and signal intensities is feasible and reliable, providing an objective measure of perianal Crohn's fistula and response to treatment.

Keywords: fistula: Crohn's disease, MRI

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Introduction

One third of all Crohn's disease (CD) patients develop perianal fistula,¹ representing a distinct and aggressive phenotype,² causing pain and discharge that results in reduced quality of life.³ The disease course is often severe and disabling, involving multiple medical and surgical interventions.^{1,4,5} Established treatment principles involve a multidisciplinary approach,⁶ aggressively

managing proctitis, judicious use of surgery to drain sepsis, and optimising medical Crohn's treatment through a combination of antibiotics, immunosuppressants and anti-tumour necrosis factor (TNF) therapies.

Response to treatment can be assessed in a variety of ways. The most common scoring tools and techniques used include: fistula drainage assessment

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(FDA; described below); perianal disease activity index (PDAD);⁷ Crohn's disease activity index (CDAI);⁸ inflammatory bowel disease questionnaire (IBDQ)⁹ and magnetic resonance imaging (MRI).⁸ The current standard of clinical response to treatment is the FDA as used in the ACCENT II trial, which defines remission as 'complete cessation of drainage from all fistula openings present at baseline despite gentle finger pressure, on at least two occasions over at least a 4 week period, and improvement as a 50% reduction in the number of external openings present or draining'.¹⁰ CD is a chronic relapsing and remitting disease as are its fistulising complications,¹¹ so clinical remission cannot be determined at individual time points, as the very nature of discharge is sporadic. Furthermore, closure of an external opening does not necessarily equate to deep healing of the tracts,¹² or indeed improved quality of life.⁸

Pelvic MRI has been shown to be the most accurate method for classification of the primary tract and secondary extensions;¹³ the recognition and treatment of the latter being essential to ensure satisfactory healing.¹⁴ MRI scans inform clinicians about fistula complexity, for example, the number of tracts, presence of undrained sepsis and the patients' response to treatment interventions. Importantly, MRI can evaluate deep tissue healing, which cannot be clinically assessed.⁸

Assessment of radiological improvement is subjective and wide variation exists between radiologists. Previous attempts to standardize radiological response, such as the Van Assche system, have been criticised due to insensitivity to change,^{8,12} and represent descriptive scores rather than monitoring tools. Currently, there is no universally accepted or reliable method of monitoring long-term radiological response to treatment. However, it is our view that clinical monitoring alone is inadequate. Proper evaluation of interventions for perianal Crohn's fistula requires accurate monitoring of response, as does the development of tools that will enable prediction of successful treatment. Future research and development therefore needs to focus on accurate forms of imaging to provide standardized, responsive and accurate tools to assess radiological response to treatment.

The imaging module of the recently published fistulising CD core outcome set comprises two outcomes, 'Fistula response on imaging' and 'an

activity-based MRI score responsive to change'.¹⁵ At present, perianal fistula complexity on MRI is judged based on fistula configuration, involvement of adjacent pelvic spaces, presence of undrained sepsis and volume.^{8,12,16,17} Whilst the first three components are based on anatomical assessment, there is currently no method to calculate fistula volume and it is not performed in routine practice. We hypothesize that volume change is an important measure of fistula response that may be incorporated as part of a core measurement set.

This pilot study aims to confirm the feasibility of objectively calculating perianal fistula volume using segmentation software through evaluation of repeatability, reproducibility and comparison with the current standard of subjective assessment of MRI fistula response.

Methods

Ethics

All patients were treated on the basis of clinical need according to standard clinical care at our institution, on an open-label basis and according to licensed or published regimens. After consultation with the local research and development (R&D) department (London North West Healthcare NHS Trust), it was advised that approval by a National Health Service (NHS) research ethics committee or the R&D department was deemed unnecessary owing to the non-patient identifiable retrospective nature of this feasibility study. The study received departmental approval by the research lead of St Mark's Hospital, London, United Kingdom. The study was registered as a service evaluation and all patients were treated only after full and informed clinical consent as part of routine care, and therefore research consent was not required.

Patients and setting

We performed a retrospective analysis of patients with perianal Crohn's fistula selected using a random number generator from a cohort treated at St. Mark's Hospital, UK between 2007 and 2013. Adult patients were selected if they met the following inclusion criteria: perianal Crohn's fistula; current anti-TNF α treatment (infliximab or adalimumab); and had two MRI studies >1 year apart. MRI scans were performed twice a year following biological therapy and then annually as

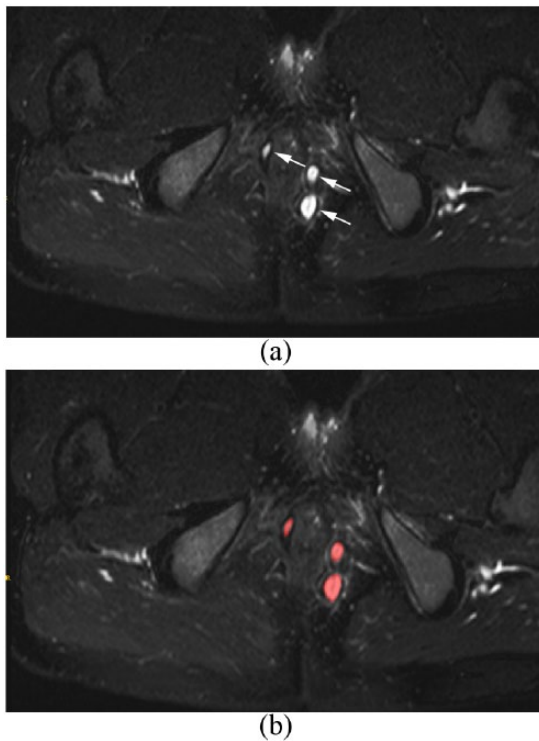


Figure 1. Example of manual segmentation of a perianal fistula. (a) An axial fat saturated T2 weighted image showing a complex high signal fistula (arrows). (b) The same image with the fistula having been manually segmented (now highlighted in red).

part of the St Mark's fistula protocol. A cohort of 18 patients were selected using a random number generator by one of the authors (NY) for this pilot study as a previous paper was able to assess inter-observer variability on assessment of fistula scoring in a group of this size. Patient demographic data were retrieved.

MRI technique

Standard axial T2-weighted Spectral Attenuated Inversion Recovery (SPAIR) MRI sequences were acquired (TR 8000; TE96; thickness 4 mm; gap 0.2 mm; FOV 240 mm; averages 4, flip angle 150, bandwidth 130 Hz/PX). Digital imaging and communications in medicine images of the MRI sequences were retrieved from the picture archiving and communication system and anonymized.

MRI evaluation

Perianal fistulas were defined as tubular structures that abnormally connected the enteric

lumen to the skin and the borders defined as the transition between T2 high signal and low signal fibrosis/fat on fat suppressed sequences. Each fistula tract at baseline and follow up was assessed and characteristics documented by reader, PL. Fistula characteristics included: fistula type based on the Park's classification; simple or branched fistula configuration; supralelevator or ischioanal fossa involvement; presence of horseshoe configuration; presence of interstitial high signal surrounding the fistula tract; and presence of proctitis.

A total of two specialist gastrointestinal radiologists (PL and JB with 7 and 3 years' experience) measured fistula volumes, signal intensity and time taken to measure fistula volumes on baseline and follow-up MRI scans using ITK-SNAP (version 2.2.0), a validated Open Source segmentation software¹⁸ (Figure 1). All contents within the borders of the fistula were considered part of the fistula volume. Reader PL repeated the readings for MRI studies after 2 months.

To minimize bias, three experienced, specialist gastrointestinal radiologists (PL, AG, DB with 7, 12 and 15 years' experience) also assessed fistula response to treatment (improved, worse or unchanged) by comparing baseline and follow-up MRI scans for each patient.

Statistics

Inter and intra-observer correlation for measurement of fistula volumes were assessed using intra-class correlation (ICC). Subsequent analysis of fistula volume was performed using data from reader PL.

Agreement between specialist gastrointestinal radiologists for fistula response to treatment was assessed using the kappa statistic. Consensus agreement was taken if two or more radiologists agreed. Differences in percentage volume change for each category of radiologist assessed fistula response to treatment were assessed using the Kruskal–Wallis test, for each reader and also for the consensus.

The Mann–Whitney test was used to compare percentage volume change with fistula characteristics with only two categories, whilst the Kruskal–Wallis test was used where there were more than two categories.

Table 1. Patient fistula characteristics and their association with percentage volume change.

Variable	N	Median % volume change (IQR)	p-value
Fistula tract type			
Intersphincteric	3	514 [-78, 559]	0.63
Transsphincteric	12	-5 [-61, 301]	
Extrasphincteric	3	-55 [-67, 217]	
Configuration			
Solitary	4	337 [54, 523]	0.34
Branched	14	-30 [-67, 217]	
Supralelevator/ischioanal involvement			
No	3	515 [-78, 559]	0.37
Yes	15	-17 [-67, 217]	
Horseshoe sepsis			
No	9	186 [-47, 487]	0.20
Yes	9	-42 [-74, 17]	
Peri-fistula interstitial high signal			
No	6	-47 [-74, 416]	0.88
Yes	12	6 [-17, 217]	
Proctitis			
No	13	6 [-55, 416]	0.59
Yes	5	-42 [-82, 217]	
IQR, interquartile range.			

Results

A total of 18 patients (12 men, 6 women) with Crohn's perianal fistula were recruited with median age of 29 years (range 19–52 years). At baseline, they had a total of 23 fistula tracts; 13 with single tracts only and 5 with two fistula tracts. 15 of 23 (65%) tracts were transsphincteric, 5 (22%) were intersphincteric and 3 (13%) were extrasphincteric. A total of seven patients had proctitis. Fistula characteristics during the course of this study are detailed in Table 1.

Average time taken to calculate volume measurements was 3 min 22 sec and 4 min 10 sec for readers 1 and 2 respectively with moderate agreement (ICC 0.73) in time taken between readers.

Inter-observer variability between readers was very good for volume and mean signal intensity with ICC of 0.95 [95% confidence interval (CI) 0.91–0.98] and 0.95 (95% CI 0.90–0.97) respectively. Intra-observer variability was also very good for volume and mean signal intensity with ICC of 0.99 (95% CI 0.97–0.99) and 0.98 (95% CI 0.95–0.99) respectively.

There was good agreement for assessment of subjective fistula response between all three radiologists (kappa 0.69; 95% CI: 0.49–0.90), with all (100%) cases agreed by at least two radiologists and most (13/18; 72%) agreed by all three radiologists.

Manual segmentation measuring percentage change in fistula volume was significantly associated with

Table 2. Categorical patient and disease factors, and their association with fistula volume change.

Variable	Category	N	Mean fistula % volume percentage change (SD)	p-value
Gender				
	Male	12	-5 [-66, 337]	0.71
	Female	6	85 [-67, 416]	
Site affected at presentation				
	Perianal disease only	7	-7 [-67, 217]	0.62
	Perianal + luminal disease	11	6 [-74, 487]	
Biologic therapy				
	Infliximab	12	-45 [-70, 216]	0.16
	Adalimumab	6	201 [6, 559]	
Thiopurines				
	No	5	-47 [-78, 6]	0.30
	Yes	13	17 [-55, 416]	
SD, standard deviation.				

subjective assessment of radiological response to treatment by all three radiologists ($p = 0.001$). The calculated median volume change was -67% [interquartile range (IQR): $-78, -47$], 0% (IQR: $-16, +17$), and $+487\%$ (IQR: $+217, +559$) for fistulas assessed by radiologists as improved, stable or worsening respectively.

Percentage volume change measured by manual segmentation was not associated with any of the fistula characteristics assessed by radiology (Table 1).

The observed difference in median percentage change in fistula volume between infliximab and adalimumab, -45% (IQR: $-70\%, +216\%$) and $+201\%$ (IQR: $+6\%, +559\%$) did not reach significance ($p = 0.16$).

No significant association was found between the categorical (Table 2) and continuous (Table 3) variables relating to participants' CD and percentage volume change.

Discussion

MRI is the gold standard test for assessment of perianal Crohn's fistula and subjective assessment of change in fistula volume is frequently

reported to help determine response to treatment, particularly for Gastroenterologists assessing the impact of drug treatment.^{8,12} However, there has been no objective method for quantification of fistula volume and this has therefore not been included in MRI scoring systems to date.^{8,12,17,19} Studies of surgical treatment have also struggled to identify a robust, objective measure of radiological improvement.²⁰ The present study has shown that volume of perianal fistula in patients with CD can be reliably measured by MRI with very good inter- and intra-observer agreement. Objective measurement of volume is facilitated by the sharp boundary between high intensity fistula and the surrounding low intensity fat or scar tissue (fibrosis), which can be perceived easily by the human observer.

Manual measurement of fistula volume took a relatively short time (up to 4 min 10 sec) with the difference between readers likely related to experience. The authors acknowledge that any significant delay in reporting times limits generalizability and warrants scrutiny, and therefore determination of the additional clinical benefit of precise volume measurement over subjective assessment will be required. That said, objective fistula volume measurement can be applied to very

Table 3. Continuous patient and disease factors, and their association with fistula volume measurement.

Variable	Correlation coefficient	p-value
Age	-0.02	0.95
Year of Crohn's diagnosis	0.11	0.65
Time between Crohn's diagnosis and scan	-0.08	0.74
Year of fistula diagnosis	0.08	0.75
Time between fistula diagnosis and scan	-0.08	0.74
Length of time between scans	-0.17	0.51

complex disease that involve multiple tracts and collections, which are usually more difficult to assess subjectively. Furthermore, it will be possible to automate measurement of fistula volume in the future, negating any impact on reporting times and enabling less experienced observers to assess fistula volume more accurately.

We found good inter-observer agreement for the subjective assessment of fistula response on MRI indicating that it represents a good standard against which to assess volume as objective measures. We also demonstrated minimal inter and intra-observer variability in volume measurement indicating this represents a consistent and repeatable measure. We investigated the association between change in fistula volume and subjective assessment of fistula response by experienced gastrointestinal (GI) radiologists at St. Mark's Hospital, UK. We found strong agreement between this objective measure and the subjective assessment (Figure 2).

Having determined that volume demonstrates good inter- and intra-observer variability, is quick to perform and correlates well with the current standard of subjective assessment of improvement when performed by experienced GI radiologists, we plan to investigate the relationship of these radiological measures of change with clinical outcomes in larger longitudinal and prospective studies. Such studies will require larger groups of consecutive patients so that correlation between clinical and radiological change can be assessed. Furthermore, whilst not within the scope of this pilot study, new drugs and surgical techniques may also be evaluated using objective fistula volume measurement.

Despite good agreement overall, disagreement between readers for individual patient assessments are noteworthy. One fistula with an objective 17% increase in volume was reported as 'no change' by two readers and 'worse' by one reader. When reviewed retrospectively, all readers agreed there was a mixed response where different component of the fistula increased and decreased in volume over time. Similarly, another fistula had nearly healed bar a subcutaneous fluid focus, which had increased in size leading to an overall 6% increase in fistula volume. These cases reinforce the need to assess additional fistula characteristics, beyond volume alone, when judging response to treatment. Notably, our study also found that these additional characteristics (Table 1) are independent of percentage volume change (implying that scoring systems based on description of these characteristics may remain insensitive to change, and that specific fistula configurations do not appear to obviate the utility of this technique, although larger studies are required to confirm these).

We believe that accurate assessment of reduction in inflammation and volume is key to the clinical utility of this technique. One hypothesis is that the rate and/or extent of volume reduction in a given period following treatment (at 3 months from induction, for example), will predict the rate and completeness of fistula closure, the duration of remission or the risk of fistula recurrence. This would be beneficial in stratifying patients undergoing expensive treatment with significant adverse effects.

Although we did not find significant correlation between fistula volume and clinical findings, we

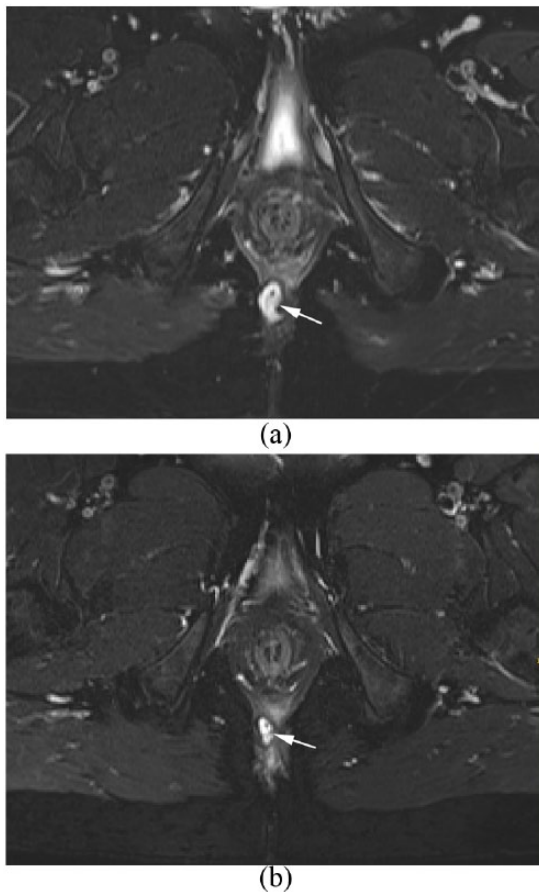


Figure 2. This perianal fistula [arrows] at similar levels shows a subjective improvement between baseline (a) and follow up (b). Manual segmentation is able to quantify this difference with a -42% percentage change in fistula volume.

suspect this is related to the small sample size and heterogeneous cohort. This pilot work was designed to develop the volume measurement technique and was not powered to detect such a correlation with clinical findings.

The present study has several limitations, including a small sample size and its retrospective design. However, it confirms the feasibility of our technique to measure perianal fistula volumes. Additionally, the standard with which we compared our objective measurement is subjective and complete agreement between all three assessors was not observed. Nevertheless, agreement between them was strong and as experienced, specialist GI radiologists their subjective assessment represents the best currently available standard with which to compare volume assessments.

Conclusion

Quantification of fistula volumes is feasible and reliable, with the potential to provide objective measurement of perianal Crohn's fistula and response to treatment. This is the first step towards developing an objective and responsive MRI based volume score.

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1. Sahnan K, Lung PFC, Adegbola SO, Burling D, Burn J, Tozer PJ, Gupta A, Faiz OD, Phillips RKS, Hart AL. An objective measure of response to treatment for patients with Crohn's perianal fistulas on anti-TNF treatment. European Crohn's & Colitis Organisation. *Poster Presentation, 15-18th February 2017.*
2. Sahnan K, Adegbola SO, Tozer PJ, Faiz OD, Phillips RKS, Hart AL. Novel use of MRI volume measurement & 3D modelling in perianal Crohn's fistulae. 'Global Health Innovator Competition', Institute for Global Health Innovation, *Oral Presentation, 7th March 2016.*
3. Sahnan K, Phillip RKS. 3D reconstruction of perianal fistula and the use of MRI volumes. Imaging, sensing and digital in GI medicine, Enteric Hackday 2016. Invited podium presentation. *Course Convenors – Prof Knowles, Prof Williams, 14th October 2016.*

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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