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Published in:
European Journal of Radiology

DOI:
10.1016/j.ejrad.2021.110049

Publication date:
2021

European Journal of Radiology 145 (2021) 110049

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Diagnostic performance of MRI in detecting residual soft tissue sarcoma after unplanned excision: Systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Sarcoma
Reoperation
Magnetic resonance imaging
Sensitivity and specificity
Systematic review
Meta-analysis

ABSTRACT

Objective: To investigate, in a systematic review and meta-analysis, the diagnostic performance of MRI in detecting residual disease after unplanned excision of soft tissue sarcoma.
Methods: Medline and Embase were searched for original studies on the diagnostic performance of MRI detecting residual soft tissue sarcoma after unplanned excision. Study quality was assessed using QUADAS-2. Sensitivity and specificity were pooled using a bivariate random-effects model. A Chi-squared test was used to test for heterogeneity.
Results: Ten studies were included, comprising a total of 469 patients. Median frequency of residual soft tissue sarcoma was 54.6% (range 31.6–73.1%). There was high risk of bias with respect to flow and timing in one study. There were applicability concerns with respect to patient selection in four studies. Nine studies reported to use the presence of a mass as a diagnostic criterion for residual soft tissue sarcoma. Sensitivities of included studies ranged between 36.4% and 86.7%, and specificities ranged between 77.8% and 100%. Pooled sensitivity was 65.9% (95% confidence interval [CI]: 55.5–74.9%) and pooled specificity was 85.1% (95% CI: 79.1–89.6%). The area under the summary receiver operating characteristic curve was 0.852. The included studies were statistically heterogeneous in their estimates of sensitivity ($P = 0.016$) and statistically homogeneous in their estimates of specificity ($P = 0.793$).
Conclusion: The presence of a mass is the most commonly reported diagnostic criterion to diagnose residual soft tissue sarcoma after unplanned resection. MRI achieves moderate sensitivity and fairly high specificity. Pooled estimate of sensitivity was subject to heterogeneity, which needs further exploration.

1. Introduction

Soft tissue sarcomas are a heterogeneous group of neoplasms arising from mesenchymal tissue [1,2]. Curative treatment consists of complete resection, with or without adjuvant therapy [2]. Soft tissue sarcomas are rare, with an age-adjusted incidence rate of 2.4 per 100,000 per year [1]. It is estimated that only one out of every 200–300 superficial soft tissue lumps is a soft tissue sarcoma [3]. Not surprisingly, some superficial soft tissue sarcomas may initially be mistaken for benign lesions in clinical practice. This can lead to an unplanned nononcologic excision (also known as a "whoops" procedure [3]) which occurs in approximately 30% of patients with extremity soft tissue sarcoma [2]. Unplanned excisions are frequently inadequate, with residual tumor in 35–74% of patients [3]. Re-excision should be performed to achieve complete tumor removal [2,3]. Because re-excision is usually more extensive and associated with considerably more morbidity [2], it should ideally be avoided in patients who do not have residual tumor. It is often difficult to accurately assess the pathological margins and extent of the initial, unplanned resection [4]. MRI may be used to assess whether residual tumor is present and whether or not there is an indication for re-excision. To our knowledge, however, the diagnostic performance of MRI in detecting residual tumor is not completely clear. Therefore, the objective of our study was to investigate, in a systematic review and meta-analysis, the diagnostic performance of MRI in detecting residual disease after unplanned excision of soft tissue sarcoma.

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https://doi.org/10.1016/j.ejrad.2021.110049
Received 9 August 2021; Received in revised form 6 September 2021; Accepted 15 November 2021
Available online 16 November 2021
0720-048X/

2. Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline [5].

2.1. Literature search

Medline and Embase were searched for original studies which reported the diagnostic performance of MRI in detecting residual soft tissue sarcoma after unplanned excision. The following search term was used: ((soft AND tissue) AND (sarcoma OR sarcomas OR tumor OR tumours OR malignancy)) OR Whoops) AND residual AND (magnetic resonance OR MR imaging OR MRI OR magnetic resonance tomography OR nuclear magnetic resonance OR NMR). Abstracts, reviews, guidelines, and studies with fewer than 10 patients, were excluded. Furthermore, we excluded studies which only reported the diagnostic performance of MRI in detecting locally recurrent soft tissue sarcoma in the follow-up after an initially properly planned oncological excision. Studies which provided insufficient data to construct a 2 × 2 contingency table to calculate sensitivity and specificity on a per-patient basis, were also excluded. The search was updated until August 1, 2021. There were no language restrictions.

2.2. Data extraction

Principal study characteristics (publication year, country of origin, number, age and sex of included patients, soft tissue sarcoma types, time interval between initial excision and MRI, time interval between MRI and re-excision, use of neoadjuvant therapy before re-excision, reference standard used, and frequency of residual soft tissue sarcoma were extracted. Data on the MRI protocol used, the diagnostic criteria for residual disease, the qualification of MRI readers, and the numbers of true positive, false positive, false negative, and true negative MRI scans for residual soft tissue sarcoma were also extracted.

2.3. Study quality

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool [6] was used to assess the methodological quality of each included study.

2.4. Statistical analyses

Sensitivity and specificity of MRI were calculated for each included study. Sensitivity and specificity were pooled using a bivariate random-effects model [7]. Sensitivity and specificity of individual studies and summary estimate with 95% confidence ellipse were plotted in receiver operating characteristic (ROC) space [7]. A Chi-squared test was performed to test for heterogeneity (defined as $P < 0.10$). Statistical analyses were performed using Microsoft Excel and Meta-analysis of Diagnostic Accuracy Studies package in R software [8,9].

3. Results

3.1. Literature search

The flow diagram of the study selection process is displayed in Fig. 1. The search yielded 225 articles in Medline and 358 articles in Embase. After reading the titles and abstracts, 12 studies remained. The full text version of one Chinese article could not be retrieved, despite contacting the authors [10]. After reading the full text version of the 11 remaining studies, one study was excluded because the diagnostic performance of MRI in detecting residual soft tissue sarcoma after unplanned excision was not investigated [11]. Eventually, 10 studies remained and were included [4,12–20] (Fig. 1). The principal characteristics of these studies are displayed in Table 1. The median number of patients per study was 37 (range 21–111), resulting in a total of 469 patients. The far majority

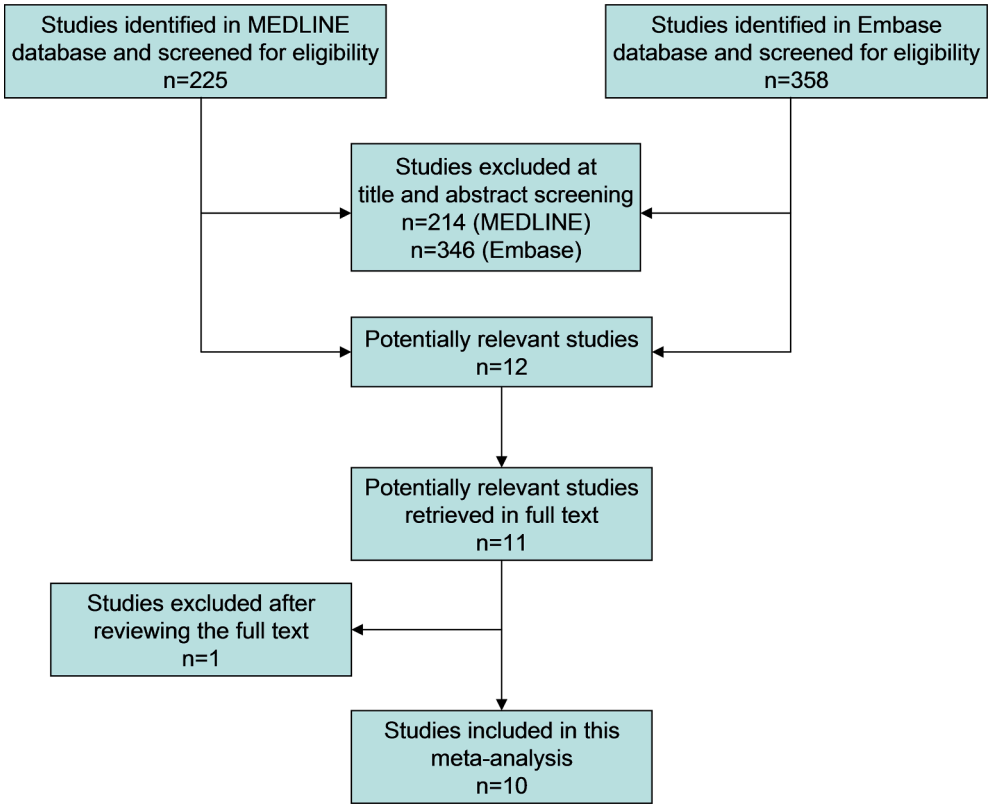

Fig. 1. Flow diagram of the study selection process.

Table 1
Principal characteristics of the included studies.

Study	Publication Year	Country	No. of included patients, age and sex	Location of soft tissue sarcoma (no.)	Soft tissue sarcoma types (no.)	-Time interval between initial excision and MRI -Interval between MRI and re-excision -Neoadjuvant therapy before re-excision	Reference standard	Frequency of residual soft tissue sarcoma
Alramdan [12]	2021	The Netherlands	26, median age 64.5 years (range 21–98), 19 males	Arm (6), leg (7), back (5), chest wall (4), abdominal wall (2), gluteal area (2).	Myxofibrosarcoma (8), leiomyosarcoma (5), pleomorphic sarcoma (4), synovial sarcoma (4), dermatofibrosarcoma (1), liposarcoma (1), myofibroblastic sarcoma (1), extraskeletal osteosarcoma (1), rhabdomyosarcoma (1)	-NR -NR -No	Pathologic findings after re-excision	19/26 (73.1%)
Erol [13]	2020	Turkey	50, mean age 47.3 years (±22,9), 28 males	Upper extremity (16), lower extremity (33), thoracic (1)	NS	-NR -NR -Yes (3 patients)	Pathologic findings after re-excision	34/50 (68.0%)
Wang [14]	2017	USA	21, mean age 58 years (range 29–79), 13 males	Shoulder (2), upper arm (1), elbow (1), forearm (1), wrist (1), thumb (2), thigh (6), knee (4), lower leg (2), first toe (1)	Myxofibrosarcoma (7), pleiomorphic liposarcoma (1), dermatofibrosacroma protuberans (1), rhabdomyosarcoma (1), epitheloid sarcoma (1), unclassified sarcoma (2), fibrosarcoma arising in dermatofibrosarcoma protuberans (1), acral myxoinflammatory fibroblastic sarcoma (1), pleomorphic fibroblastic/-myofibroblastic sarcoma (1), synovial sarcoma (1), myxoid liposarcoma (1), leiomyosarcoma (1), pleomorphic myofibroblastic sarcoma (1), pleomorphic fibroblastic sarcoma (1)	-Median 2.9 months (range 0.1–10.1) -NR -Yes (12 patients)	Pathologic findings after re-excision	11/21 (52.3%)
Patkar [4]	2016	India	55, mean age 40 years (range 18–72), 30 males	Upper extremity (9), lower extremity (44), back (2)	Synovial sarcoma (10), spindle cell sarcoma (9), dermatofibrosarcoma (2), leiomyosarcoma (2), myxofibrosarcoma (2), clear cell sarcoma (1), epitheloid sarcoma (1), liposarcoma (1), malignant periperal nerve sheath tumor (1)	-Median 30 days -Median 60 days -NR	Pathologic findings after re-excision	28/55 (50.9%)
Gingrich [15]	2017	USA	76, median age 55 years (range 6–86), 48 males	Extremity (56), trunk (20)	High-grade undifferentiated pleomorphic sarcoma (20), liposarcoma (16), leiomyosarcoma (9), malignant peripheral nerve sheath tumor (8), dermatofibrosarcoma protuberans (4), other (19)	-NR -NR -Yes (6 patients)	Pathologic findings after re-excision	45/64 (70.3%)
Kim [16]	2016	South Korea	38, mean age 50.5 years (range 16–84), 16 males	Shoulder (56), elbow (2), forearm (5), hand (1), thigh (12), knee (5), lower leg (3), axilla (1), chest wall (4), back (1), buttock (1), inguinal area (2)	Liposarcoma (8), leiomyosarcoma (5), dermatofibrosarcoma protuberans (4), malignant peripheral nerve sheath tumor (3), undifferentiated pleomorphic sarcoma (3), myxofibrosarcoma (2), extraskeletal osteosarcoma (2), rhabdomyosarcoma (2), soft-tissue metastasis (2), squamous cell carcinoma (2), melanoma (1), synovial sarcoma (1), sarcomatoid	-Mean 42.3 days (range 7–90) -NR -NR	Pathologic findings after re-excision (21 patients) or clinical/ imaging follow-up at 3, 6 and 12 months (17 patients)	12/38 (31.6%)

(*continued on next page*)

Table 1 (*continued*)

Study	Publication Year	Country	No. of included patients, age and sex	Location of soft tissue sarcoma (no.)	Soft tissue sarcoma types (no.)	-Time interval between initial excision and MRI -Interval between MRI and re-excision -Neoadjuvant therapy before re-excision	Reference standard	Frequency of residual soft tissue sarcoma
					carcinoma (1), lymphoma (1), Merkel cell carcinoma (1)			
Choi [17]	2013	South Korea	35, mean age 48 years (range 18–78), 17 males	Shoulders (3), arms (3), elbow (1), finger (1), thigh (11), legs (2), knee (1), feet (4), toe (1), supraclavicular area (1), axilla (1), chest wall (1), back (2), buttock (2), inguinal area (1)	Liposarcoma (10), undifferentiated pleomorphic sarcoma (7), leiomyosarcoma (5), dermatofibrosarcoma protuberans (3), squamous cell cancer (2), synovial sarcoma (2), fibrosarcoma (2), epithelioid soft-tissue tumor (1), melanoma (1), clear cell sarcoma (1), malignant peripheral nerve sheath tumor (1)	-Mean 21 days (range 4–64) -NR -NR	Pathologic findings after re-excision	14/35 (40.0%)
Puhaindran [18]	2010	USA	33, mean age 37 years (range 8–80), 18 males	Hand (33)	Epithelioid sarcoma (8), synovial sarcoma (6), undifferentiated pleomorphic sarcoma (5), leiomyosarcoma (2), liposarcoma (2), myxofibrosarcoma (2), angiomatoid fibrous histiocytoma (1), clear cell sarcoma (1), fibrosarcoma (1), dermatofibrosarcoma protuberans (1), malignant peripheral nerve sheath tumor (1), acral myxoinflammatory fibroblastic sarcoma (1), plexiform fibrohistiocytic tumor (1), ossifying fibromyxoid tumor (1)	– – –	Pathologic findings after re-excision	15/33 (45.5%)
Davies [19]	2004	UK	111, mean age 48 years (range 5–87), 63 males	Thigh (20), ankle and foot (16), others NS	NR	-Median 33 days (range 9–458) -NR -NR	Pathologic findings after re-excision	63/111 (56.8%)
Kaste [20]	2002	USA	24, median age 13 years (range 0–19), 11 males	Arm (3), hand (1), hip (1), thigh (7), leg (2), knee (6), foot (2), face (1), abdomen (1)	Synovial sarcoma (8), malignant schwannoma (3), malignant fibrous histiocytoma (2), malignant hemangiopericytoma (2), spindle cell sarcoma (2), dermatofibrosarcoma protuberans (1), alveolar soft part sarcoma (1), liposarcoma (1), paraganglioma (1), clear cell sarcoma (1), leiomyosarcoma (1), and malignant peripheral nerve sheath tumor (1)	-Median 15.5 days (range 1–330) -NR -NR	Pathologic findings after re-excision	14/24 (58.3%)

NR: not reported.
NS: not specified.

of soft tissue sarcomas was located in the extremities, followed by the chest wall/back. In one study the location of soft tissue sarcomas was not completely specified [19], Only one study reported inclusion of a patient with soft tissue sarcoma located in the abdomen [20]. Median frequency of residual soft tissue sarcoma per included study was 54.6% (range 31.6–73.1%).

3.2. Study quality

Study quality assessment is summarized in Fig. 2. Risk of bias with respect to patient selection was rated low in all ten included studies [4,12–20]. Risk of bias with respect to index test was rated unclear in five studies [4,13,15,16,19], because these studies did not report whether interpretation of MRI was blinded to the reference standard. Similarly, risk of bias with respect to reference standard was rated unclear in all ten included studies [4,12–20], because none reported whether interpretation of the reference standard was blinded to MRI findings. Risk of bias with respect to flow and timing was rated high in one study [16], because not all included patients received the same reference standard (pathologic findings after re-excision served as

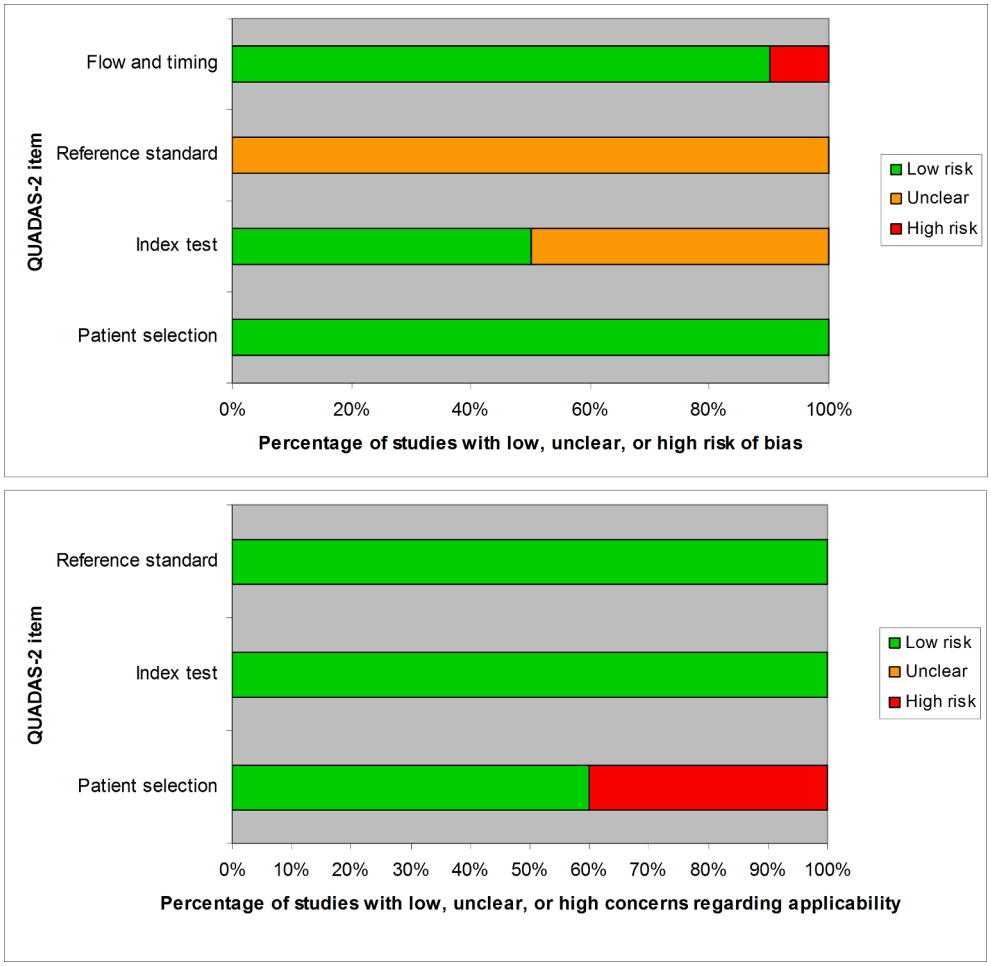

Fig. 2. Summary of QUADAS-2 assessments.

reference standard in 21 patients, whereas clinical/imaging follow-up served as reference standard in the remaining 17 patients). There were applicability concerns with respect to patient selection in four studies because two of these studies also included some patients who underwent neoadjuvant therapy before re-excision [13,14] and two other studies [4,17] also included a few patients with other soft tissue malignancies than sarcoma (Table 1). There were no other applicability concerns.

3.3. Diagnostic performance of MRI

Nine studies used the presence of a mass as a diagnostic criterion for residual soft tissue sarcoma (Table 2, Fig. 3). Only one study did not report the diagnostic criteria they used [13]. Sensitivities of included studies ranged between 36.4% and 86.7%, and specificities ranged between 77.8% and 100% (Table 2). Pooled sensitivity was 65.9% (95% confidence interval [CI]: 55.5–74.9%) and pooled specificity was 85.1% (95% CI: 79.1–89.6%). The corresponding ROC plot is shown in Fig. 4. The area under the summary ROC curve was 0.852. The included studies were statistically heterogeneous in their estimates of sensitivity (P = 0.016) and statistically homogeneous in their estimates of specificity (P = 0.793).

4. Discussion

We systematically reviewed the performance of MRI in diagnosing residual soft tissue sarcoma after unplanned excision. Slightly more than half of the included patients (median frequency of 54.6%) had residual disease based on pathologic findings after re-excision. The presence of a mass was the most commonly reported criterion to diagnose residual soft tissue sarcoma with use of MRI. All included studies that specified their MRI protocol used gadolinium-enhanced MRI for mass detection. Meta-analysis of the 10 included studies showed that MRI achieves moderate sensitivity (pooled estimate of 65.9%) and fairly high specificity (pooled estimate of 85.1%). The pooled estimate of sensitivity was subject to heterogeneity, whereas the pooled estimate of specificity was statistically homogeneous. Possible explanations for the statistical heterogeneity of sensitivities across studies include differences in soft tissue sarcoma types, extent of unplanned initial excision, time interval between initial unplanned excision and MRI, and experience of interpreter (s). However, because of lack of detailed reporting and the relatively limited number of included studies, we could not perform meaningful subgroup analyses to explore potential sources of heterogeneity.

Using the QUADAS-2 tool, we encountered verification bias in one study [16], because included patients received different reference standards, consisting of pathological analysis after re-resection and clinical/imaging follow-up. There was patient spectrum bias in four studies, because these studies also included some patients who underwent neoadjuvant therapy before re-excision [13,14] and some patients with other soft tissue malignancies than sarcoma [4,17]. In addition, in 4 of the included studies [12,14,16,17], MRI was reviewed by consensus of two interpreters, which does not mirror the independent readings that radiologists typically perform in clinical practice. Interobserver agreement for residual tumor at MRI was reported by only one study and was reported to be perfect (κ value of 1.00) [2]. Future studies should overcome the above methodological shortcomings and further investigate the observer reproducibility.

Table 2
Diagnostic performance of MRI in detecting residual soft tissue sarcoma after unplanned excision.

Study	MRI protocol	Interpreter(s)	Diagnostic criterion for residual soft tissue sarcoma	Sensitivity	Specificity
Alramdan [12]	Standard~ + Gd	Two musculoskeletal radiologists, both with more than 5 years of experience in the evaluation of sarcomas, in consensus	Contrast-enhancing nodular lesion or mass	47.4%	100%
Erol [13]	NR	NR	NR	61.4%	81.3%
Wang [14]	Standard + Gd	A fellowship-trained musculoskeletal radiologist with 4 years' experience in consensus with a senior radiology resident	Nodular or mass-like enhancement	36.4%	80.0%
Patkar [4]	Standard + Gd (Gd was not used in all patients)	A senior radiologist specialized in musculoskeletal oncology	Focal mass of high signal on T2-weighted and STIR sequences	86.7% *	90.9%*
Gingrich [15]	NR	Multi-disciplinary tumor board	Focal or discrete enhancing mass	81.3%$	84.6%$
Kim [16]	Standard + Gd + DWI + DCE	Two musculoskeletal radiologists with 12 and 4 years' experience, in consensus	Definite nodule or mass formation	50.0%	88.5%
Choi [17]	Standard + Gd	Two musculoskeletal radiologists in consensus	Focally delineated enhancing portion	64.3%	90.5%
Puhaindran [18]	NR	Musculoskeletal radiologists with experience imaging sarcomas	Apparent residual mass was either present or highly suspected	80.0%	77.8%
Davies [19]	Standard + Gd (Gd was not used in all patients)	One of two experienced musculoskeletal radiologists	A soft tissue mass, hyperintense on T2-weighted and STIR images which was not uniformly homogeneous.	64.4%#	93.3%#
Kaste [20]	Standard + Gd (Gd was not used in all patients)	One pediatric radiologist	Definable soft tissue mass	75.0% ^	85.7%^
Pooled value				**65.9% (55.5–74.9%)** Chi-square 0.016	**85.1% (79.1–89.6%)** Chi-square 0.793

~ T1-weighted and (fat-suppressed) T2-weighted sequences.
* Three patients with indeterminate findings on MRI not included in accuracy analysis.
$ Nineteen patients with indeterminate findings on MRI not included in accuracy analysis.
# Seven patients with indeterminate findings on MRI not included in accuracy analysis.
^ Nine patients with indeterminate findings on MRI not included in accuracy analysis.

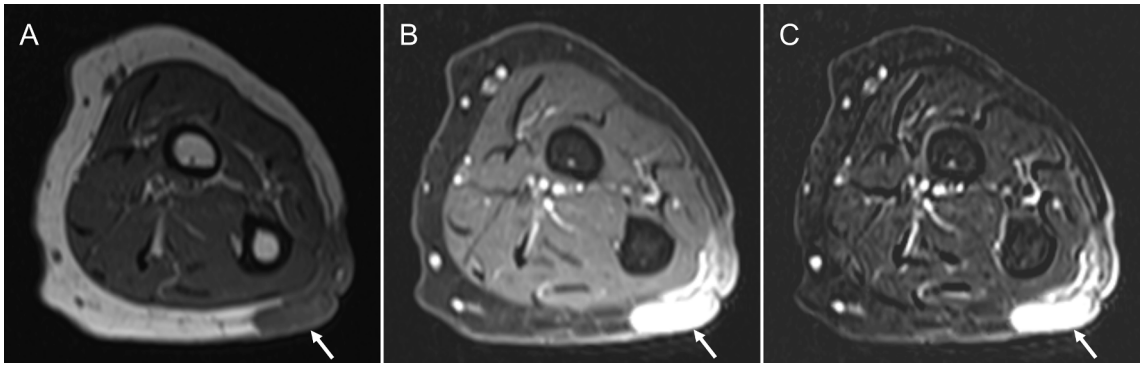

Fig. 3. Residual soft tissue sarcoma in a 98-year-old woman who underwent unplanned excision of a myofibrosarcoma at an outside institution. Axial T1-weighted image (A), post Dotarem T1-weighted image with fat suppression (B), and subtraction post-Dotarem T1-weighted image (C) show a subcutaneous enhancing mass at the ulnar side of the left forearm (arrows). Findings are compatible with residual soft tissue sarcoma, which was confirmed pathologically after re-excision.

Our results show that MRI cannot reliably exclude residual soft tissue sarcoma, which is explainable by the limited resolution of MRI. Unplanned excisions can be categorized as R0 resection (i.e. microscopic complete tumor resection), R1 resection (i.e. macroscopic complete tumor resection but microscopically positive margins), or R2 resection (i.e. a partial, piecemeal, or incisional resection with macroscopic residual tumor) [21]. Although patients with microscopic residual disease are at increased risk of local recurrence, it has been reported that does not occur in approximately 72% of these patients [22]. Recent research has shown that a watch and wait approach for re-excision after unplanned, yet macroscopically complete excision of soft tissue sarcoma may be safe and may not affect metastatic risk or amputation rate [23]. In this regard, it may be important to differentiate R2 resection from R1/R0 resection. However, none of the included studies provided diagnostic performance data specified by R1/R0, and R2 status. This remains a topic for future study. Specificity of MRI was fairly high but not perfect, which may be explained by the presence of postoperative hematoma, granulation tissue or scarring which could in some cases be mistaken for residual soft tissue sarcoma [12,17,16,24]. Specificity may be improved by using image subtraction in gadolinium-enhanced MRI [12], diffusion-weighted (DW) MRI, and/or dynamic contrast-enhanced (DCE) MRI [16,24]. Only one of the studies included in our systematic review investigated the potential value of DW MRI and DCE MRI [16]. Their results showed that apparent diffusion coefficient (ADC) values were significantly associated with the presence of residual tumor, as were DCE MRI parameters [16]. However, DW images including ADC maps were of insufficient diagnostic quality in a non- negligible number of patients, especially when lesions were superficially located, of small

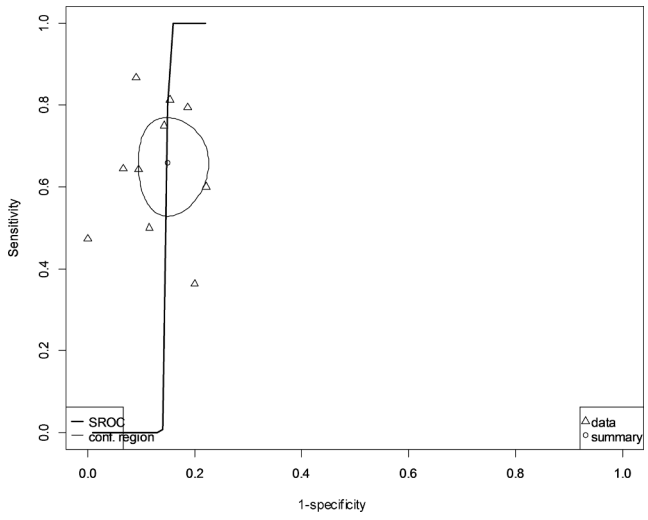

Fig. 4. Receiver operating characteristic plot. SROC: summary receiver operating characteristic curve conf. region: 95% confidence ellipse of pooled sensitivity and specificity.

size, or affected by motion artefact [16]. More independent studies are needed to further explore the added value of DW MRI and DCE MRI to a standard MRI protocol (including gadolinium-enhanced images) for the assessment of residual soft tissue sarcoma. MRI provides superior soft tissue contrast and is currently the imaging modality of choice to detect residual soft tissue sarcoma. However, resolution is relatively limited. The same holds true for ultrasonography, CT, and positron emission tomography (PET), which also cannot exclude the presence of microscopic residual disease. The combination of PET and MRI could improve accuracy, but this remains to be investigated.

Our study has some limitations. First, although our study attempted to synthesize the findings of multiple individual studies, we could not formally explore potential sources of heterogeneity in sensitivity (including soft tissue sarcoma subtypes). Second, because we included only 10 studies, we could not reliably assess whether publication bias may have been present.

In conclusion, the presence of a mass is the most commonly reported diagnostic criterion to diagnose residual soft tissue sarcoma after unplanned resection. MRI achieves moderate sensitivity and fairly high specificity. Pooled estimate of sensitivity was subject to heterogeneity, which needs further exploration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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