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The diagnostic significance of repeat ultrasound-guided biopsy of musculoskeletal soft-tissue lesions with initially inconclusive biopsy results

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A B S T R A C T

Introduction: To determine the diagnostic yield of repeat ultrasound (US)-guided biopsy of musculoskeletal soft-tissue lesions with initially inconclusive biopsy results, and to explore predictive factors for success of repeat biopsy.

Materials and methods: This retrospective study included 42 patients who underwent a repeat (second) US-guided biopsy session to target a musculoskeletal soft-tissue lesion because an initial US-guided biopsy session provided inconclusive results. Both biopsy sessions were performed in a tertiary referral center for soft-tissue sarcomas.

Results: The diagnostic yield of repeat US-guided biopsy was 47.6%. Malignant nature of the lesion ($P = 0.031$), sharp lesion borders on US ($P = 0.011$), and good to very good lesion visibility on US ($P = 0.017$) were significantly associated with a diagnostic repeat US-guided biopsy. There was also a trend towards significance ($P = 0.073$) for a higher number of biopsy passes through the lesion. Other patient characteristics (age and gender), magnetic resonance imaging features (lesion homogeneity on T1-weighted, T2-weighted, and gadolinium chelate enhanced sequences, borders, enhancement pattern, depth and size), US features (lesion appearance, vascular flow, and depth), biopsy-related factors (days between initial and repeat US-guided biopsy, needle diameter, maximum length of acquired samples), and operator-related factors (same or different radiologists/pathologists for initial and repeat biopsies), were not associated with the diagnostic success of the repeat US-guided biopsy.

Conclusions: Repeat US-guided biopsy of a musculoskeletal soft-tissue lesion with initially inconclusive biopsy results can be useful to establish a final diagnosis. Lesion features on US (borders and visibility) may be used to prospectively determine the utility of a repeat US-guided biopsy.

Introduction

Soft-tissue tumors and tumor-like lesions in the extremities or trunk are frequently encountered in clinical practice [1]. Ultrasonography (US) and magnetic resonance imaging (MRI) are useful to characterize some lesions as benign (such as ganglia, bursae, or lipomas) without any need for biopsy or follow-up [1]. However, US and MRI are frequently not able to differentiate between the wide spectrum of non-neoplastic conditions and benign tumors vs. malignant tumors [1–4]. In these cases, tissue sampling is required to establish a diagnosis [1–4].

Biopsy of a soft-tissue mass should be performed in a specialized sarcoma center. Percutaneous US-guided biopsy is the method of choice for initial tissue sampling of superficial musculoskeletal soft-tissue lesions and is preferred over more invasive open surgical

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biopsy. Biopsy under computed tomography (CT) guidance is also possible, but this is usually reserved for deep-seated lesions (i.e., lesions that are difficult to target by US) and also involves the use of potentially harmful ionizing radiation [5,6]. Overall, the diagnostic yield of percutaneous US-guided biopsy for musculoskeletal soft-tissue lesions has been reported to be around 87% [7]. However, a problem arises when the acquired tissue is reported to be inadequate or inconclusive by the pathologist to establish a diagnosis. There may be several causes of inconclusive biopsy results, including inadequate biopsy technique, or an underlying specific pathologic process that is difficult to diagnose on the basis of a small amount of tissue [8]. In these patients with inconclusive biopsy results, a repeat (second) US-guided biopsy session may be performed. If diagnostically successful, this repeat US-guided biopsy session has the advantage of sparing patients more invasive and costlier open surgical biopsy or follow-up imaging (if opted for) that may cause patients' anxiety. However, if not diagnostically successful, a repeat US-guided biopsy session may cause further diagnostic delay, results in a longer period of anxiety for the patient, and also entails costs.

At present, the clinical role of repeat US-guided biopsy of musculoskeletal soft-tissue lesions has not been defined yet due to a lack of data on its diagnostic yield. Although previous studies have addressed the topic of repeat biopsy of musculoskeletal lesions, they suffered from small sample sizes, mixed soft-tissue lesions with bone lesions, and mixed US- and CT-guided biopsies [9,10]. Furthermore, it is still unknown if there are any factors associated with a high or low diagnostic yield of repeat US-guided biopsy of musculoskeletal soft-tissue lesions. This knowledge may be useful to decide which patients may benefit from a repeat US-guided biopsy and which patients should directly undergo open surgical biopsy or follow-up imaging.

The purpose of this study was therefore to determine the diagnostic yield of repeat US-guided biopsy of musculoskeletal soft-tissue lesions after initially inconclusive biopsy results, and to explore factors associated with the diagnostic success of the second biopsy.

Materials and methods

Study design

This retrospective single-center study was approved by the local institutional review board (IRB number: 201800105), and the requirement for informed consent was waived. Our hospital is a tertiary referral center for soft-tissue sarcomas, in which suspicious soft-tissue masses are biopsied under imaging guidance, in line with national guidelines. Percutaneous US-guided biopsy is the initial approach for tissue sampling of all superficial musculoskeletal soft-tissue lesions. The database of our hospital was searched, within a consecutive 10-year period (November 2007 to November 2017), for all patients who had undergone a repeat (second) US-guided biopsy session to target a musculoskeletal soft-tissue lesion because an initial US-guided biopsy session yielded inconclusive results (i.e., a specific diagnosis in terms of benignancy or malignancy could not be made). Both initial and repeat biopsy sessions were performed in our hospital. Patients with a suspicion of a recurrence of a previously known and/or treated tumor were excluded. Lesions that were biopsied under CT guidance, bone lesions with a soft-tissue component, non-musculoskeletal lesions (e.g., breast, thyroid, liver, etc.), and extravisceral masses inside the thoracic of abdominal cavity were also excluded. Chest wall lesions and abdominal wall lesions were not excluded.

MRI acquisition

MRI scans were performed using different clinical 1.5-T and 3.0-T MRI systems, and applied sequences were adapted to body region of interest and lesion size. Furthermore, some MRI scans were performed elsewhere before referral to our institution. Therefore, MRI protocols were not homogeneous. Sequences or reconstructed images (in case a three-dimensional isotropic MRI sequence was acquired) had to be oriented in at least two perpendicular directions with regard to the lesion, to be eligible for analysis. T1-weighted, (fat-suppressed) T2-weighted, and gadolinium chelate enhanced sequences were analyzed in this study. Otherwise, there were no predefined protocol criteria for MRI scans to be included in the analysis.

US acquisition and US-guided biopsy

All lesions were first ultrasonographically assessed and then biopsied in the same session under US guidance by 20 different radiologists (of whom 9 with musculoskeletal expertise and 11 general radiologists) using two US systems (Toshiba, Xario XG or Siemens Acuson S2000) with 8–14 MHz transducers. Twenty-nine out of 42 repeat biopsy sessions were performed by a different radiologist than for the initial biopsy session. All biopsies were performed under sterile conditions. After local anesthesia with 10 mL lidocaine (1%), a small skin cut was made through which the biopsy needle was inserted. All biopsies were targeted at solid-appearing parts of the lesion of interest, while avoiding cystic or necrotic areas. This was done by using available magnetic resonance images and US guidance. Tru-cut core needle biopsies were performed using a BioPince needle (Angiotech Pharmaceuticals) with variable needle diameters (range: 16-18G), stroke lengths (13, 23, or 33 mm), and variable number of acquired samples, at the discretion of the musculoskeletal radiologist who performed or supervised the biopsy procedure. The biopsy needle had to pierce the lesion on US (or presumed location based on surrounding anatomic landmarks if poorly visible), and the acquired tissue cores had to be judged as sufficient based on visual (macroscopic) inspection, before the biopsy procedure was terminated. There was no minimum required number of biopsy passes through the lesion and there was no pathologist on site to evaluate the adequacy of the acquired tissue specimens. Representative US images of the lesion were captured and stored in the Picture Archiving and Communication System (PACS).

MRI and US review

Magnetic resonance and US images were reviewed by a radiologist (T.C.K., with 7 years of experience in musculoskeletal imaging) who was blinded to all histopathological and follow-up data, using a PACS workstation (Carestream Vue PACS version 11.4.1.1102, Carestream Health, Inc).

The following lesion characteristics were assessed on MRI: lesion appearance on T1-weighted, T2-weighted, and gadolinium chelate enhanced sequences (homogeneous vs. inhomogeneous), lesion borders on T1-weighted, (fat-suppressed) T2-weighted, and gadolinium chelate enhanced sequences (sharp vs. unsharp), lesion enhancement pattern (A. non-enhancement or only rim-enhancement of a surrounding pseudo-capsule; B. peripheral enhancement with non-enhancing central area; C. diffuse enhancing mass with scattered non-enhancing areas and/or enhancement bridges; or D. completely homogeneous enhancement, as described previously for contrast-enhanced ultrasonography [11]), lesion depth (measured as the shortest distance from the skin to the nearest outer border of the lesion on gadolinium chelate enhanced or T2-weighted sequences), and lesion size (largest diameter in any plane on gadolinium chelate enhanced or T2-weighted sequences).

The following lesion characteristics were assessed on US: lesion appearance on B-mode US (homogeneous vs. inhomogeneous), lesion borders on B-mode US (sharp vs, unsharp), vascular flow in the lesion on power or colour doppler US (present vs. absent), lesion depth on B-mode US (measured as the shortest distance from the skin to the nearest outer border of the lesion), and lesion visibility compared to background on B-mode US (poor to moderate vs. good to very good).

Presence of biopsy-related complications (based on the radiology report and electronic patient file) was also determined.

Histopathological examination

All acquired tissue specimens were evaluated by an expert musculoskeletal pathologist (A.J.H.S.) with more than 30 years of experience in the diagnosis of soft-tissue tumors. Repeat US-guided biopsies were considered diagnostic if they yielded a specific benign or malignant diagnosis, whereas repeat US-guided biopsies were considered non-diagnostic if they yielded insufficient material to establish a specific diagnosis.

Reference standard

The final diagnosis of each lesion was determined based on all available tissue specimens from biopsy or surgery. Each lesion was then classified as benign or malignant. If a final diagnosis could not be made based on histopathology, clinical and imaging follow-up were used to determine the nature of the lesion in terms of benignancy or malignancy. Lesions that decreased in size during follow-up without any treatment, were considered benign. Lesions that remained stable during a follow-up of at least one year, were also considered benign. The nature of all other lesions was considered unclear.

Statistical analysis

The percentage of repeat US-guided biopsies that were diagnostic (i.e., diagnostic yield) was calculated, along with 95% confidence intervals (CIs). Furthermore, the following variables were compared between diagnostic and non-diagnostic repeat US-guided biopsies, using the Fisher's exact test for binary data, the Mann-Whitney *U* test for non-Gaussian continuous data, and the independent samples *t*-test for Gaussian continuous data: patient characteristics (age and gender), nature of the lesion in terms of benignancy or malignancy, MRI features (lesion appearance, borders, enhancement pattern, depth and size), US features (lesion appearance, borders, vascular flow, depth, and lesion visibility), biopsy-related factors (days between initial and repeat US-guided biopsy, needle diameter, number of biopsy passes through the lesion, and maximum length of acquired core sample for initial and repeat biopsies), and operators who performed and interpreted the biopsies (same or different radiologists/pathologists for initial and repeat biopsies). Shapiro-Wilk tests were first used to check whether continuous variables in the different groups were normally distributed. *P*-values <0.05 were considered statistically significant. Statistical analyses were executed using dedicated software (IBM Statistical Package for the Social Sciences version 24.0).

Results

Patients

Between November 2007 and November 2017, a total of 590 consecutive superficial musculoskeletal soft-tissue lesions were percutaneously biopsied under US guidance. Fig. 1 provides an overview of these 590 US-guided biopsies, their diagnostic outcome and the subsequent management of non-diagnostic biopsies. A total of 42 patients (21 men and 21 women; median age of 52 years; age range of 15–82 years) who underwent a repeat (second) US-guided biopsy session to target a musculoskeletal soft-tissue lesion because an initial inconclusive biopsy result, were included. Median time between the initial and repeat biopsy was 22.5 days (range: 3–220 days). Characteristics of included patients are shown in Table 1.

MRI

MRI was performed in 39 out of 42 patients who were finally

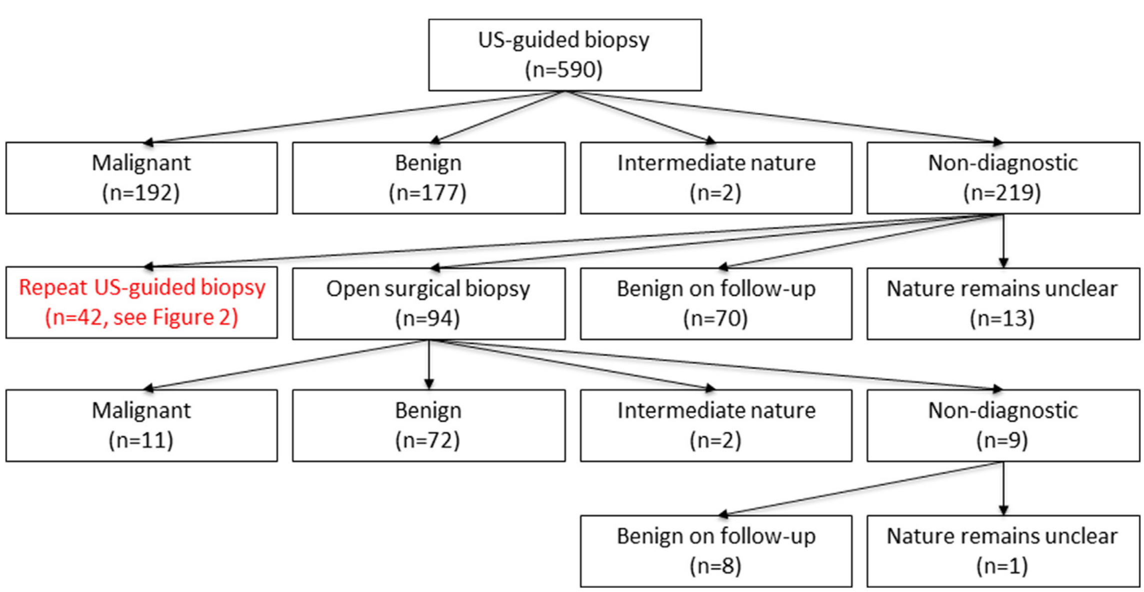

Fig. 1. Overview of all 590 consecutive percutaneous US-guided biopsies of musculoskeletal soft-tissue lesions performed within a 10-year period at our institution, their diagnostic outcome and the subsequent management of non-diagnostic biopsies.

Table 1
Characteristics of included patients.

Number of patients	42
Median age (years) with range	51 (15–82)
Males/females	21/21
Number of lesions and US-guided biopsies	42
Number of lesions in different anatomic sites	
-Upper leg	12 (28.6%)
-Upper arm	10 (23.8%)
-Knee	8 (19.0%)
-Lower arm	3 (7.1%)
-Lower leg	3 (7.1%)
-Abdominal wall	1 (2.4%)
-Back	1 (2.4%)
-Elbow	1 (2.4%)
-Foot	1 (2.4%)
-Hand	1 (2.4%)
-Paratesticular	1 (2.4%)

included. T1-weighted, (fat-suppressed) T2-weighted, and gadolinium chelate enhanced sequences were available in 38, 38, and 34 cases, respectively. Applied slice thicknesses varied between 0.8 mm and 6.0 mm.

Diagnostic yield repeat US-guided biopsy

Repeat US-guided biopsies were diagnostic in 20 lesions and non-diagnostic in 22 lesions, which corresponds to a diagnostic yield of 47.6% (95% CI: 33.4–62.3%). There were no reported biopsy-related complications. Lesions with a diagnostic repeat biopsy were located in the upper leg (n = 7), upper arm (n = 5), knee (n = 4), lower arm (n = 1), hand (n = 1), abdominal wall (n = 1), and lower leg (n = 1). Lesions with a non-diagnostic repeat biopsy were located in the upper arm (n = 5), upper leg (n = 5), knee (n = 4), lower arm (n = 2), lower leg (n = 2), elbow (n = 1), back (n = 1), paratesticular soft tissue (n = 1), and foot (n = 1).

Of the 20 lesions with diagnostic repeat US-guided biopsy results, 11 (55.0%) were benign, 8 (40.0%) malignant, and 1 (5.0%) was of intermediate biologic nature (Fig. 2 and Table 2). Subsequent surgical resection was performed on 5 malignant lesions, 9 benign lesions, and 1 lesion of intermediate biologic nature, which did not change the diagnosis in any of these lesions.

Of the 22 lesions with non-diagnostic repeat US-guided biopsy results, 18 lesions (81.8%) eventually proved to be benign (based on subsequent surgical resection [n = 11] or follow-up [n = 7]), 2 lesions (9.1%) eventually proved to be malignant (based on a third diagnostic US-guided biopsy and subsequent surgical resection [n = 1] or subsequent surgical resection only [n = 1]), and 2 lesions (9.1%) remained of unclear nature despite subsequent surgical exploration (Fig. 2 and Table 3).

Table 2
Yield of 20 repeat (second) US-guided biopsies with diagnostic histopathology results.

Nature lesion	Specific diagnosis
Malignant (n = 8)	-Extranodal diffuse large B-cell lymphoma (n = 1)
	-Extraosseous Ewing sarcoma (n = 1)
	-Grade 1 myxoid liposarcoma (n = 1)
	-Grade 2 myxofibrosarcoma (n = 1)
	-High-grade undifferentiated pleomorphic fibrosarcoma (n = 1)
	-Plasmablastic lymphoma (n = 1)
	-Pleomorphic liposarcoma (n = 1)
	-Well-differentiated inflammatory leiomyosarcoma (n = 1)
Benign (n = 11)	-Giant cell tumor (n = 3)
	-Abscess (n = 2)
	-Arteriovenous malformation (n = 1)
	-Desmoid-type fibromatosis (n = 1)
	-Inflamed epidermal cyst (n = 1)
	-Intramuscular myxoma (n = 1)
	-Neurofibroma (n = 1)
	-Schwannoma (n = 1)
Intermediate (n = 1)	-Angiomatoid fibrous histiocytoma [n = 1]

Factors associated with the diagnostic success of the repeat US-guided biopsy

Malignant nature of the lesion ($P = 0.031$), sharp lesion borders on US ($P = 0.011$), and good to very good visibility of the lesion on US ($P = 0.017$) were significantly associated with a diagnostically successful repeat US-guided biopsy. There was also a trend towards significance ($P = 0.073$) for a higher number of biopsy passes through the lesion for diagnostic repeat biopsies compared to non-diagnostic repeat biopsies. All other patient, MRI, US, biopsy-related, and operator-related factors were not significantly associated with the diagnostic success of the repeat US-guided biopsy (Table 4). Representative images are shown in Figs. 3 and 4..

Discussion

The results of this study show that almost half of patients with an indeterminate pathology result after an initial biopsy session of a musculoskeletal soft-tissue lesion, benefit from a repeat (second) US-guided biopsy session, because it allows the establishment of a specific diagnosis, without any complications. Of 20 diagnostic repeat biopsies, 8 (40.0%) were malignant, 11 (55.0%) were benign, and 1 (5.0%) was of intermediate nature. Subsequent surgical resection (if performed) did not change the diagnosis in any of these patients. These patients can thus be spared an open surgical biopsy that is more invasive with associated potential complications and costs. Another important new finding of this study is that

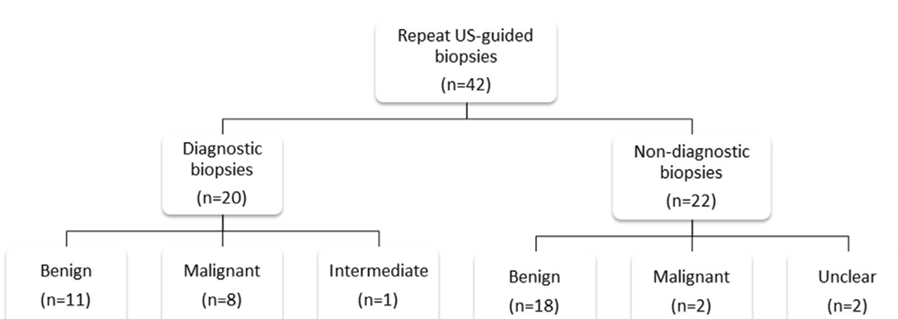

Fig. 2. Outcome of 42 repeat US-guided biopsies.

Table 3
Eventual outcome of 22 repeat (second) US-guided biopsies with non-diagnostic histopathology results.

Nature lesion	Specific diagnosis
Malignant (n = 2)	-Malignant peripheral nerve sheath tumor (n = 1) -Well-differentiated liposarcoma (n = 1)
Benign (n = 18)	-Unspecified diagnosis (n = 4) -Hematoma (n = 3) -Cavernous hemangioma (n = 1) -Complex cyst with chronic synovitis after biceps tendon rupture (n = 1) -Desmoid-type fibromatosis (n = 1) -Extra-osseous aneurysmal "bone" cyst (n = 1) -Giant cell tumor (n = 1) -Intramuscular myxoma (n = 1) -Lateral epicondylitis (n = 1) -Lipoma (n = 1) -Post-traumatic soft-tissue changes due to adjacent fracture (n = 1) -Spindle cell lipoma (n = 1) -Synovial chondromatosis (n = 1)
Unclear (n = 2)	-"Complex vascular lesion with focal thrombosis" -"Inflammatory changes and thrombus material"

Table 4
Patient characteristics, MRI and US lesion features, biopsy-, and operator-related factors of all included patients and comparison between diagnostic and non-diagnostic repeat biopsies.

Parameters	All patients (n = 42)	Diagnostic repeat biopsies (n = 20)	Non-diagnostic repeat biopsies (n = 22)	*P*-value
Age	51 (34.8–65.8)[a]	59.0 (24.8–73.0)[a]	49.0 (35.8–61.3)[a]	0.435◦
Gender (male/female)	21/21	11/9	10/12	0.758*
Nature lesion (malignant/benign)	10/29[+]	8/11	2/18	0.031*
T1-weighted MRI lesion appearance (homogeneous/inhomogeneous)	24/14[1]	14/5	10/9	0.313*
T1-weighted MRI lesion borders (sharp/unsharp)	29/9[1]	15/4	14/5	1.000*
T2-weighted MRI lesion appearance (homogeneous/inhomogeneous)	13/25[1]	8/10	5/15	0.307*
T2-weighted MRI lesion borders (sharp/unsharp)	30/8[1]	16/2	14/6	0.238*
Gadolinium chelate enhanced MRI lesion appearance (homogeneous/ inhomogeneous)	13/20[2]	7/9	6/11	0.728*
Gadolinium chelate enhanced MRI lesion borders (sharp/unsharp)	24/10[3]	13/3	11/7	0.270*
Gadolinium chelate enhanced MRI lesion enhancement pattern (A/B/C/D)	4/3/17/9[2]	1/2/8/5	3/1/9/4	0.688'
MRI depth lesion (mm)	15 (9–21)[a,4]	12 (7–17)[a]	16.50 (10–30)[a]	0.083◦
MRI largest lesion diameter in any axis (mm)	55 (41–100)[a,4]	92 (45–150)[a]	45 (39–68)[a]	0.402◦
US lesion appearance (homogeneous/inhomogeneous)	18/24	10/10	8/14	0.533*
US lesion borders (sharp/unsharp)	27/15	17/3	10/12	0.011*
US internal flow lesion (yes/no)	15/19[3]	10/8	5/11	0.185*
US depth lesion (mm)	8.5 (6–14)[a]	8 (6–13)[a]	8.5 (5–18)[a]	0.704◦
US lesion visibility (poor-moderate/good-very good)	12/30	2/18	10/12	0.017*
Days between initial and repeat biopsies	22.5 (13.8 –32.3)[a]	26.6 (13.3–31.5)[a]	24.5 (13.8–35.3)[a]	0.705◦
Biopsy needle diameter (gauge) for initial biopsy	16 (16–18)[a,5]	16 (16–17)[a]	17 (16–18)[a]	0.336◦
Number of biopsy passes through the lesion for initial biopsy	3 (2–3)[a,6]	3 (2–3)[a]	3 (2–4)[a]	0.819◦
Maximum length of acquired core sample (mm) for initial biopsy	23 (23–35)[a,7]	23 (23–32)[a]	23 (–)[a]	0.429◦
Biopsy needle diameter (gauge) for repeat biopsy	16 (16–16.5)[a,8]	16 (–)[a]	16 (–)[a]	0.264◦
Number of biopsy passes through the lesion for repeat biopsy	3 (1–3)[a,7]	2 (1–3)[a]	3 (3–4)[a]	0.073
Maximum length of acquired core sample (mm) for repeat biopsy	23 (21–26)[a,9]	23 (23–28)[a]	23 (8–23)[a]	0.239◦
Radiologist (same / different radiologist performing repeat biopsy as initial biopsy)	13/29	5/15	8/14	0.514*
Pathologist (same / different pathologist interpreting repeat biopsy as initial biopsy)	21/21	10/10	11/11	1.000*

Notes:
[a]: median (interquartile range)
◦: Mann-Whitney test
*: Fisher test
': Chi-square test
[+]: One lesion of intermediate nature and two lesions whose nature remained unclear, were excluded
A. non-enhancement or only rim-enhancement of a surrounding pseudo-capsule
B. peripheral enhancement with non-enhancing central area
C. diffuse enhancement mass with scattered non-enhancing areas and/or enhancement bridges
D. completely homogeneous enhancement, as described previously
[1]: 4 missing values
[2]: 9 missing values
[3]:8 missing values
[4]: 3 missing values
[5]: 25 missing values
[6]: 15 missing values
[7]: 37 missing values
[8]: 24 missing values
[9]: 32 missing values

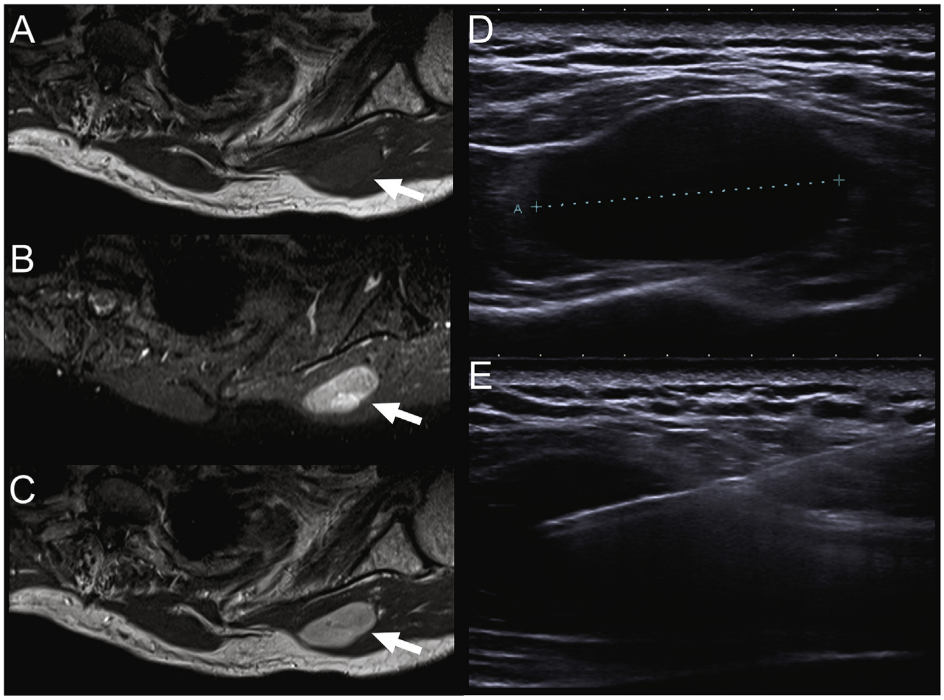

Fig. 3. A 79-year-old man without any relevant medical history underwent an FDG-PET/CT scan because of general malaise, increased serum inflammatory markers, and hypercalcemia. FDG-PET/CT (not shown) demonstrated findings consistent with polymyalgia rheumatica (increased FDG uptake around the large joints and lumbar interspinous processes), but also revealed an FDG-avid lesion in the left infraspinatus muscle. Axial T1-weighted (A), gadolinium chelate enhanced (B), and T2-weighted (C) images showed a lesion (with contrast enhancement) in the left infraspinatus muscle (arrows). The lesion had sharp borders and was well to very well visible compared to surrounding tissue on US (D), features which were found to be associated with a diagnostic repeat biopsy. The biopsy needle pierced the lesion at the time of the initial US-guided biopsy (E), but histopathology only showed non-specific findings and was considered non-diagnostic. The repeat US-guided biopsy (which was performed 41 days later) revealed a well-differentiated inflammatory leiomyosarcoma, and was therefore diagnostic. This diagnosis was confirmed after subsequent surgical resection.

if the lesion of interest exhibits sharp borders and is well visible on US, the chance of obtaining a diagnostically successful repeat US-guided biopsy appears to be higher than for those lesions that have unsharp borders and are poorly to moderately visible on US. This information can be useful to multidisciplinary sarcoma panels and patients in deciding on whether or not it is useful to pursue a repeat US-guided biopsy, or to proceed to open surgical biopsy or follow-up imaging. In addition, there was a trend towards a higher number of biopsy passes through the lesion for diagnostic repeat biopsies compared to non-diagnostic repeat biopsies, which is in line with previous work that suggested to obtain at least four specimens in soft-tissue lesions to optimize diagnostic yield [12]. Furthermore, lesions were significantly more likely benign if both the initial and repeat US-guided biopsy yielded an indeterminate pathology result. This is probably due to the fact that it is more difficult to make a definitive benign diagnosis on the basis of a small amount of tissue [8]. Importantly, however, in 2 out of 22 patients (9.1%) in whom both the initial and repeat biopsy were non-diagnostic, the lesion eventually proved to be malignant after further biopsy and/or surgical resection. This corresponds to 4.8% of all repeat US-guided biopsies. These 2 lesions were a malignant peripheral nerve sheath tumor in the right upper arm and a well-differentiated liposarcoma in the right pelvis, greater sciatic notch, and gluteal region. Sampling errors may have caused false-negative US-guided biopsy results in the former case, and difficulty in establishing the diagnosis of a well-differentiated liposarcoma from small tissue samples is the most likely explanation for the latter case. Therefore, if both initial and repeat US-guided biopsy sessions yield indeterminate pathology results, further diagnostic work-up or follow-up should not be withheld in these patients to exclude malignancy.

Until now, there has been a lack of evidence on the diagnostic yield of repeat US-guided biopsy of musculoskeletal soft-tissue lesions. The number of soft-tissue lesions included in our study is much higher compared to previous studies from the literature, such as 6 soft-tissue lesions and 20 lesions of osseous origin that were rebiopsied after an initial inconclusive biopsy in Wu et al. [9]. Furthermore, Wu et al. [9] used both US and CT for biopsy guidance. In the repeat-biopsy group, our results revealed a greater diagnostic yield (47.6%) compared to Wu et al. (38.5%) [9]. Nevertheless, the trend towards significance ($P = 0.073$) for a higher number of biopsy passes through the lesion for diagnostic repeat biopsies compared to non-diagnostic repeat biopsies is comparable to their study ($P = 0.047$). In another study by Yang et al. [10], only 5 patients with musculoskeletal lesions and initially non-diagnostic biopsies underwent repeat biopsy, which were all reported to be diagnostically successful. However, even in this limited number of 5 patients, it was unclear if they had soft-tissue or bone lesions, and if US- or CT-guided biopsies were performed [10].

The present study had several limitations. First, our study was performed in a tertiary referral center for soft-tissue sarcomas. The results of this study may be different in institutions with other patient populations, and with radiologists and pathologists who have less expertise in the management of soft-tissue tumors. Second, because of its retrospective design, there was likely selection bias. Future studies with clearly defined patient selection criteria are required to define the exact diagnostic role and cost-effectiveness of repeat US-guided biopsy compared to open surgical biopsy, in lesions with initially inconclusive results on US-guided biopsy. Third, the number of included patients was too small to perform a multivariate analysis to investigate which factors are independently associated with a diagnostically successful

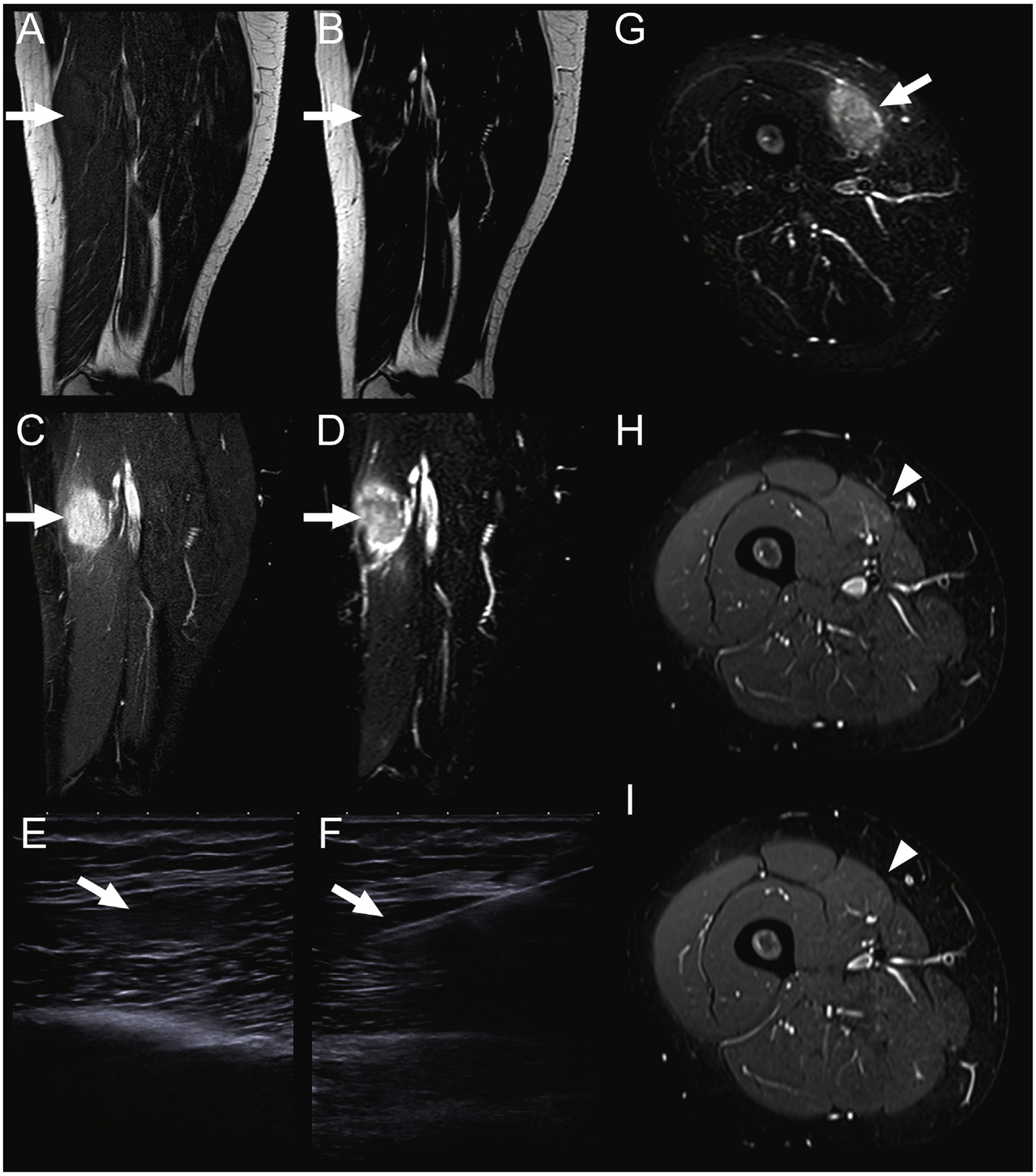

Fig. 4. A 43-year-old woman presented with muscle ache and a palpable swelling in the right upper leg. She did not have a history of trauma or overuse. Sagittal T1-weighted (A), T2-weighted (B), gadolinium chelate enhanced (C), and fat-suppressed T2-weighted (D) images showed a lesion (with contrast enhancement) in the right vastus medialis muscle (arrows). The lesion had unsharp borders and was poorly to moderately visible compared to surrounding muscle on US (E), features which were found to be associated with a non-diagnostic repeat biopsy. The biopsy needle pierced the lesion at the time of the initial US-guided biopsy (F), but histopathology only showed normal muscle tissue, and the initial biopsy was considered nondiagnostic. The repeat US-guided biopsy (which was performed 11 days later) only showed reactive fibrosis, and was also non-diagnostic. Follow-up MRI was performed. Axial fat suppressed T2-weighted images at baseline (G), 2 months (H), and 5 months (I) show complete resolution of the lesion at 2 months and 5 months (arrowheads). Therefore, the lesion was regarded benign, likely a (resolving) hematoma.

repeat US-guided biopsy. Fourth, several biopsy-related variables were missing in the radiology report. This explains why there was only a trend towards significance for an association between a higher number of biopsy passes through the lesion and a diagnostic repeat biopsy. Further studies are needed to definitely establish factors that are associated with the success of the repeat US-guided biopsy.

In conclusion, repeat US-guided biopsy of a musculoskeletal soft-tissue lesion with initially inconclusive biopsy results can be useful to establish a final diagnosis. In this series of repeat US-guided biopsies, the yield of a specific diagnosis was a little less than 50%, and in almost 5% there were false-negative results for malignancy. Lesion features on US (borders and visibility) may be used to prospectively determine the utility of a repeat US-guided biopsy.

Declarations of interest

None (all authors).

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