Cite as: Vasilevska Nikodinovska V, Ivanoski S, Kostadinova-Kunovska S, Samardziski M: Ultrasound-guided biopsy of musculoskeletal soft-tissue tumors: basic principles, usefulness and limitations. J Ultrason 2022; 22: e109–e116. doi: 10.15557/JoU.2022.0018.

Submitted: 02.01.2021
Accepted: 15.03.2021
Published: 13.04.2022

Ultrasound-guided biopsy of musculoskeletal soft-tissue tumors: basic principles, usefulness and limitations

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DOI: 10.15557/JoU.2022.0018

Keywords
soft tissue; tumor; ultrasound; core needle; biopsy

Abstract

The aim of this article is to provide a short review of the literature concerning the basic principles, usefulness and limitations of ultrasound-guided biopsy of musculoskeletal soft-tissue tumors, with particular focus on core needle biopsies. Musculoskeletal soft-tissue tumors represent a rare and complex group of heterogeneous lesions. Prompt diagnosis of these uncommon lesions can improve the outcome and increase the patient survival rate. A biopsy examination of soft-tissue tumors with imaging modalities is necessary in all cases of aggressive or undetermined lesions. Although fine needle aspiration can be helpful for the biopsy of certain tumor types, core needle biopsy is a standard procedure in most tertiary sarcoma centers. It has a high diagnostic accuracy, low complication rate and lower price in comparison to open biopsy, and can replace it in the majority of cases of soft-tissue tumor assessment. However, the examining physician has to be familiar with the technique, and the strengths and potential difficulties in performing ultrasound-guided biopsy, as well as possible solutions to obstacles. Several recently developed ultrasound techniques can be helpful and improve the outcome of imaging-guided biopsies of musculoskeletal lesions.

Introduction

Musculoskeletal (MSK) soft-tissue tumors are a complex and wide-ranging group of heterogeneous lesions. The WHO classifies soft-tissue tumors in 12 different histological groups and 4 different categories (benign, intermediate that are locally aggressive, intermediate that rarely metastasize, and malignant), depending on their biological behavior[(1)]. In addition, malignant soft-tissue tumors are very rare lesions, with an incidence of less than 1% of all malignancies[(2)]. Prompt and proper diagnosis of this large and heterogeneous group of tumors, leading to final treatment, can be essential for patient survival in cases of aggressive tumor types. A study performed by Nakamura *et al.*[(3)] examined the association between the time of symptom appearance to diagnosis with the presence of distant metastases, and the survival rate in patients with soft-tissue sarcomas. The authors concluded that the delay between the appearance of symptoms and the final diagnosis significantly influenced the development of metastases and the survival rate.

The aim of this article is to provide a short review of the literature concerning the basic principles, usefulness and limitations of ultrasound-guided biopsy of soft-tissue musculoskeletal tumors, with particular focus on core needle biopsies. A few new and emerging techniques available in the field of ultrasound-guided biopsies are also mentioned.

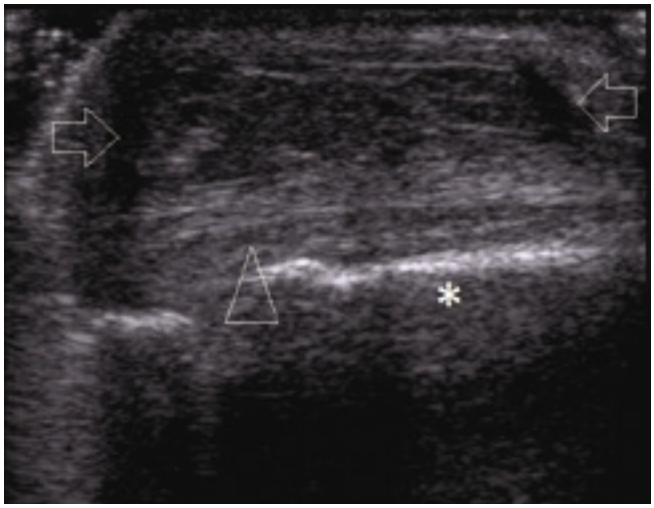

Fig. 1. *Giant cell tumor of finger flexor tendon sheath. The lesion (arrows) is visible superficially to the tendons. Flexor tendons – arrowheads; intermediate phalanx – asterisk*

Clinical and radiological evaluation

Several clinical and imaging signs are useful in discriminating between benign and malignant soft-tissue tumors, and ultrasound (US) and magnetic resonance (MRI) can aid in the diagnosis of a significant percentage of lesions.

Clinical signs, such as the presence of a firm, non-moveable, progressively growing lesion, should ring the alarm for malignancy[4,5]. Also, tumor size over 50 mm often suggests malignancy. Some of the typical benign soft-tissue tumors, but not all, frequently have a size less than 50 mm, including leiomyoma, plantar fibromatosis, and giant cell tumor of the tendon sheath[4] (Fig. 1).

With the recent advances in technology, ultrasound is recognized as the initial diagnostic method that should be used for the evaluation of soft-tissue lesions[6]. Numerous lesions have a superficial location and typical benign appearance on ultrasound[7,8]. The lesions that can be confidently diagnosed by US include superficial lipomas, simple or ganglion cysts, bursae, granulomas, fibromatosis, PNST in confirmed neurofibromatosis, and muscle hernias[7] (Fig. 2). Some juxta-articular lesions and deeply located but accessible lesions can also be examined effectively with US, and solid lesions can be reliably differentiated from cystic types[8]. However, ultrasound scanning has to be followed by cross-sectional imaging, and MRI is usually the next step in the diagnostic work-up[6], especially when lesions are localized deep to the superficial fascia, are not accessible by US, or cannot be reliably diagnosed as benign tumors sonographically[7] (Fig. 3). MRI is the technique of choice for the evaluation and local staging of soft-tissue neoplasms. It can provide valuable information about the tumor including its morphology, true size, and exact location and nearby extension, as well as the existence of satellite lesions[7]. Contrast-enhanced MRI can further improve the diagnostic accuracy in cases of soft-tissue lesions, and help in identifying the best possible site for biopsy[8].

However, in many cases, clinical and radiological signs cannot identify the type of lesion, and do not lead to the final diagnosis of soft-tissue tumor. Suspected soft-tissue lesions with an aggressive appearance or indeterminate lesions that cannot be differentiated by imaging modalities, as well as suspected MSK infections are the main indications for the next step in the diagnostic work-up, namely imaging-guided biopsy[9].

It is essential that all imaging-guided soft-tissue biopsies are performed in a tertiary sarcoma center, under a multidisciplinary team management. The lesion management in a sarcoma center can save valuable time to final diagnosis, but can also significantly increase the survival and reduce the reoccurrence rate[10].

US-guided needle biopsy: accuracy and complications

Surgical or open biopsy is still considered a gold standard for biopsy of the soft-tissue tumors. However, the recent evidences favor the use of the imaging-guided biopsy, and core needle biopsy (CNB) of soft-tissue tumors is the preferred modality recommended over the surgical biopsy in the majority of cases[6,11]. The advantages of the percutaneous

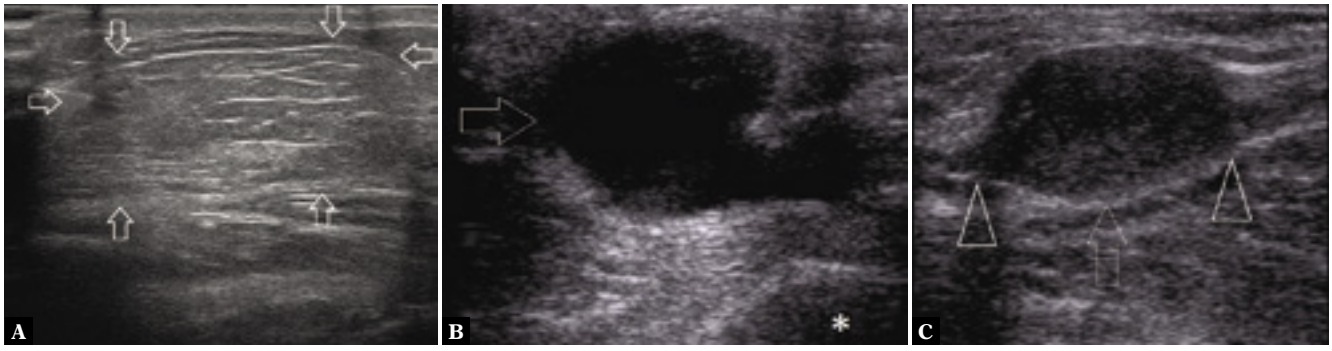

Fig. 2. A. *Typical subcutaneous lipoma (arrows). Poorly demarcated from the surrounding adipose tissue, iso/hyperechoic lesion in the subcutaneous tissue.* **B.** *Ganglion cyst of the dorsal wrist. Clearly demarcated fluid collection is depicted (arrow) arising from the dorsal radiocarpal joint space. Radius – asterisk.* **C.** *Peripheral nerve sheath tumor. Oval, hypoechoic lesion with posterior acoustic enhancement is observed (arrow), in continuity with the nerve (arrowheads)*

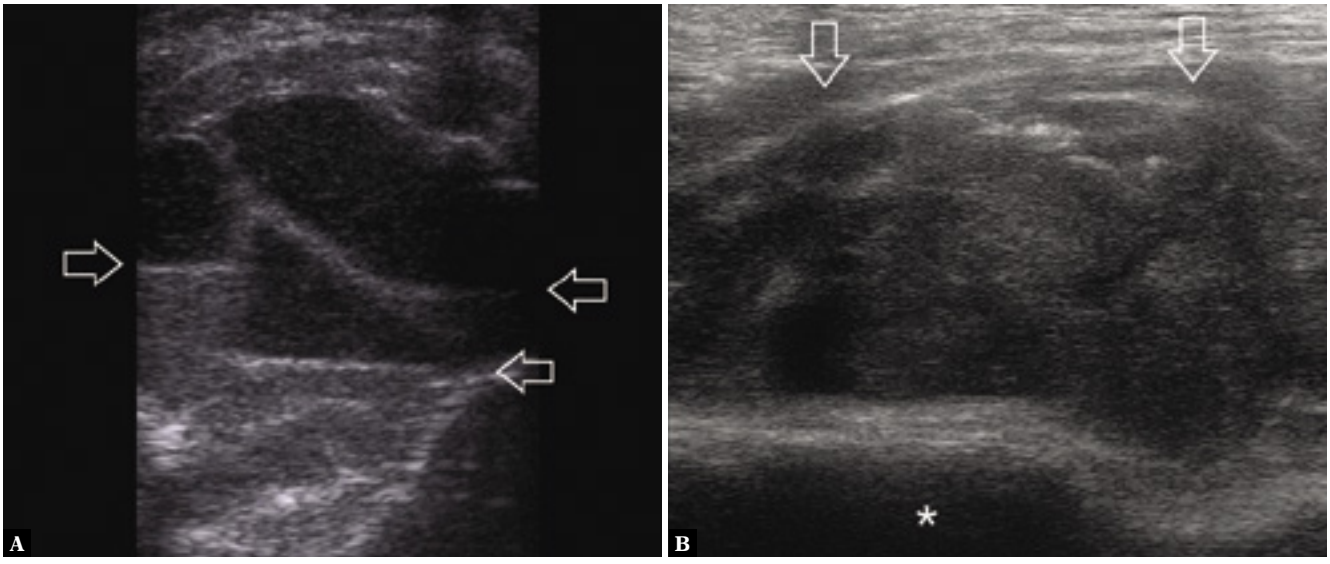

Fig. 3. A. *Paravertebral lesion with indeterminate sonographic appearance. Patient with a palpable, large, paravertebral mass sent for diagnostic ultrasound with clinical suspicion of soft-tissue tumor. Large lesion with multiple fluid-fluid levels was visualized on ultrasound (arrows), in contact with the nearby vertebra. The subsequent MRI and biopsy result (not shown) confirmed the diagnosis of aneurismal bone cyst arising from the adjacent vertebral lamina.* **B.** *Soft-tissue lesion with aggressive appearance (arrows). Solid, hypoechoic, large, intramuscular lesion located superficially to the scapula (asterisk). The biopsy result confirmed the diagnosis of high-grade rhabdomyosarcoma*

biopsy over the open (surgical) biopsy include the lower rate of complications, lower cost and shorter duration of the procedure, although a possible disadvantage is the fact that the biopsy accuracy is higher for metastatic tumors compared to primary MSK lesions[12]. Nevertheless, in a recent study by Tan *et al*.[13], evaluating the accuracy of US-guided CNB for histological grade of soft-tissue sarcoma, the concordance with the pathology result was over 96%. Metz *et al*.[14] evaluated the diagnostic rate of the imaging-guided soft-tissue biopsies in the pediatric population, with the majority of procedures being US-guided. The authors concluded that the percutaneous biopsies were safe, but also diagnostic, and provided a sufficient amount of tissue for analysis in more than 90% of the cases.

One of the main advantages of the percutaneous imaging-guided procedure is the significantly lower rate of complications, and less serious complications compared to open biopsies. A meta-analysis by Birgin *et al*.[11], including 17 studies, examined the efficacy of CNB of soft-tissue sarcoma compared to incisional biopsy. The results showed a similar diagnostic accuracy of the two methods, with a significantly lower rate of complications for the needle biopsy (1% vs 4%).

The most common potential complications of imaging-guided soft-tissue biopsies include injuries of neurovascular structures leading to bleeding (Fig. 4) and neuropraxia, and infection of the biopsy site

A serious complication of all biopsies, including the percutaneous modalities, is the possibility of tumor seeding along the needle path. The risk of track seeding with percutaneous biopsy is reported as very low, and significantly lower compared to open biopsy[15]. In a retrospective study evaluating the tumor cell contamination of the biopsy track

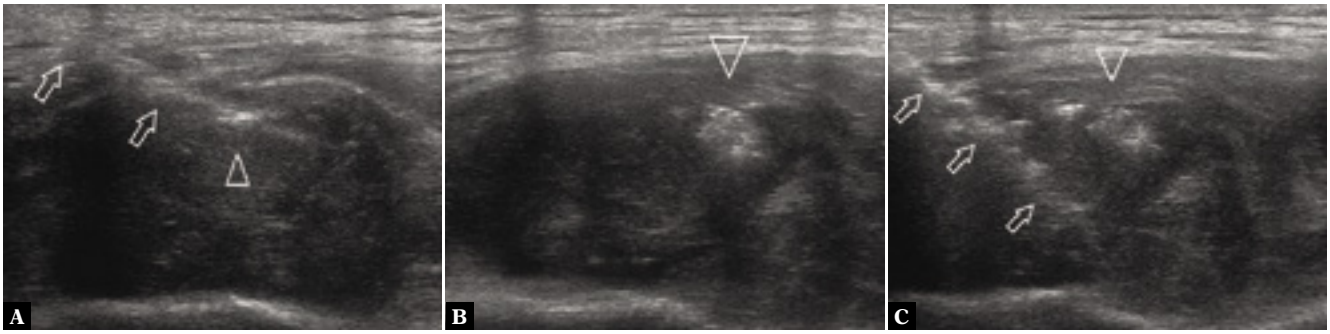

Fig. 4. *Minor complication of core needle biopsy. Discrete intratumoral hemorrhage (arrowhead) immediately after needle pass (arrows) through the peripheral vascularized tumor part (***A***). Mild hemorrhage (arrows) in the same spot a few minutes later (***B***). The hemorrhage has increased slightly (arrowhead) during the second pass through the central tumor part (arrows) (***C***). The biopsy site should be checked for significant bleeding immediately after the procedure. Routinely, minimum 5-minute local compression or compression until the bleeding ends is suggested after each core needle procedure. The patient should remain resting (sitting or lying down depending on biopsy site) in the center for observation for at least 30 minutes after the procedure*

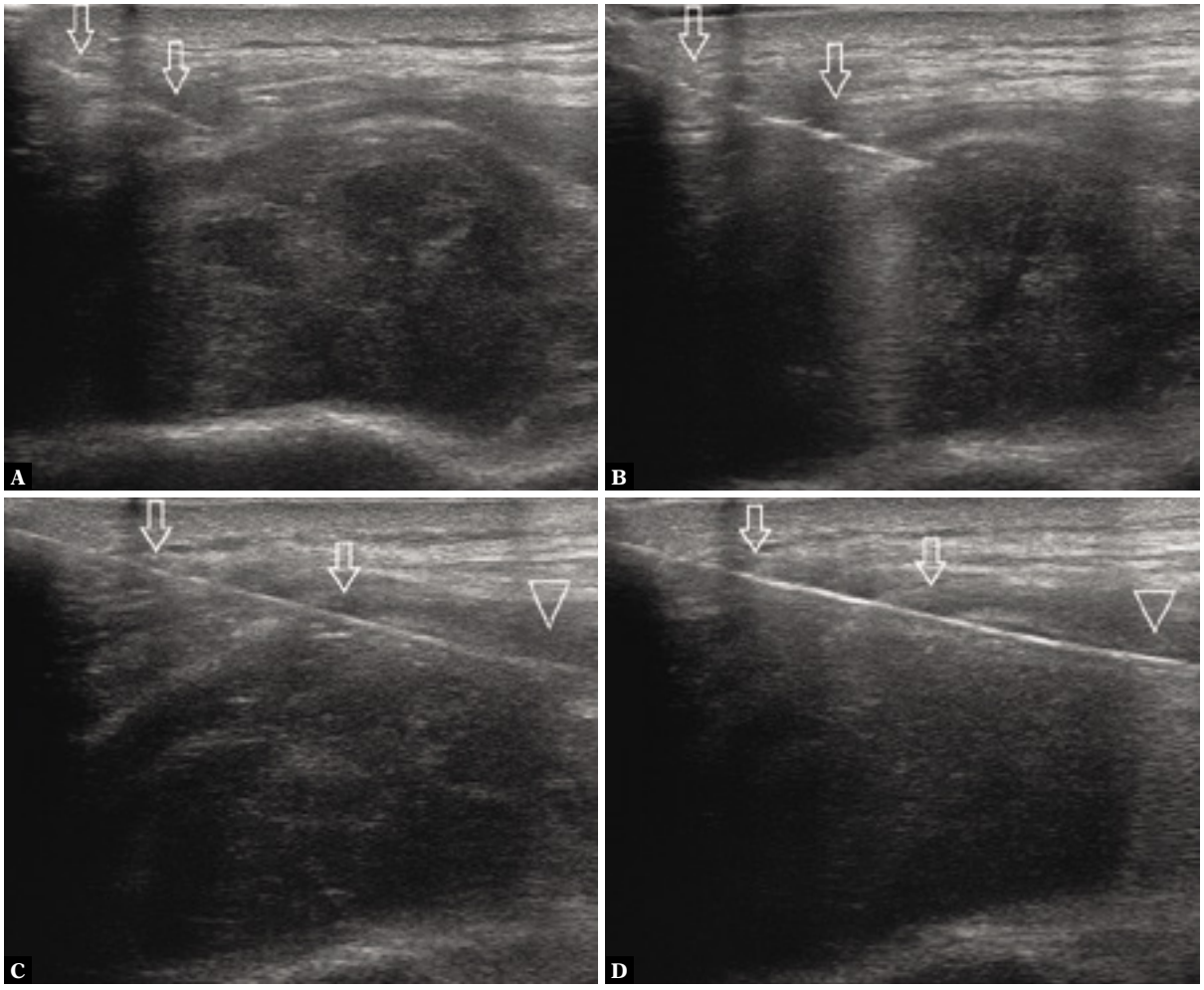

Fig. 5. *Positioning of biopsy needle and transducer. The needle should be in the same plane, as perpendicular to the transducer as possible. The needle advancement (arrows) should be followed during the entire procedure (***A, B***). There is no perfect presentation of the needle (arrows); the needle tip (arrowhead) is not clearly visible (***C***). Corrective movement – gentle rotation of the transducer can improve needle visualization (***D***). The needle is in the same longitudinal plane with the transducer, the total length of the needle is visualized (arrows), and the tip is clearly visible (arrowhead)*

in imaging-guided vs. surgical biopsy of primary MSK tumors, including 188 patients, the difference between the methods was statistically significant[15]. Histological evaluation of the track showed that there was less than 1% rate of contamination for imaging-guided biopsies and over 30% for surgical biopsies. Nevertheless, most authors report that a real risk of contamination of the biopsy track exists. The track should be removed with the final surgery of the tumor. The biopsy path of every percutaneous biopsy should be discussed with the oncologic orthopedist performing the surgery[10]. Because of the typical radial growth of the tumors within a compartment, the anatomical compartments of the extremities have to be respected, and the needle should not breach their barrier[12]. Joint contamination must be avoided.

Technical considerations for biopsy success

MSK soft-tissue biopsies are performed under local anesthesia, with only a few exceptions, such as small children or patients that are unable to cooperate or have a very low pain tolerance. In certain tumor types, like PNST, needle biopsy can cause substantial pain or nerve palsy, so proper planning and avoiding the nerve during the procedure are crucial, although sometimes difficult, so conscious sedation can be indicated[12].

Two different US techniques can be employed for biopsy guidance. In the most commonly used "in-plane" guidance method, the needle for biopsy should remain in the same plane as the transducer, and the ultrasound beam should ideally fall perpendicularly to the needle (Fig. 5A, Fig. 5B). In the "out-of-plane" method, which is less commonly used, the needle travels towards the ultrasound beam. The out-of-plane method is used in specific situations where, for example, the needle forms a very sharp angle with the beam[16] or the handling space is narrow. The needle tip has to be visualized during the procedure regardless of the technique used. One of the challenges of US-guided soft-tissue biopsies is the possible difficulty with visualization of the needle tip during the procedure (Fig. 5C, Fig. 5D), especially if

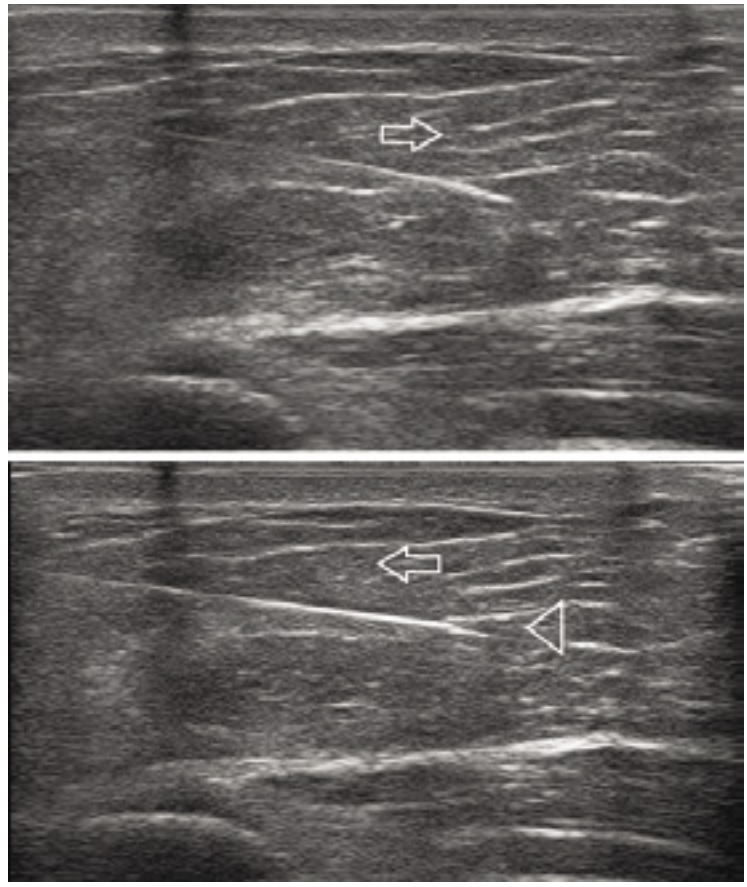

Fig. 6. *Positioning of biopsy needle for better visualization. Gentle forward and backward movement of the needle during the procedure (arrows) with the transducer remaining in the same position can help in optimizing the view of the needle and needle tip (arrowhead)*

the operator is not experienced with the US-guided biopsy procedure and equipment. Some tactics can help in better positioning and visualization, for example the presence of a small amount of air within the tip of the needle to increase its echogenicity, injecting local anesthetic during the procedure[17], gentle forward and backward needle movements (Fig. 6), or pressing the far side of the transducer instead of changing the needle angle, also known as the "heel to toe" maneuver[18].

Multiple needle passes are necessary in most cases to obtain a sufficient amount of tumor material for all pathological and immunohistochemical examinations. Wu *et al*.[19] proposed 4 passes as the peak number sufficient for obtaining an adequate tissue specimen. Repeated biopsy of previously unsuccessful US-guided CNB can be beneficial, especially if more passes are done and different sites are targeted during the second procedure. Loudini *et al*.[20] evaluated the diagnostic utility of repeated US-guided soft-tissue biopsy of previously non-diagnostic procedures, showing biopsy success in more than 45% of lesions. The authors concluded that in cases of non-diagnostic biopsy performing multiple passes, malignancy, high visibility and sharp margins of the lesion were the factors associated with the diagnostic success of repeated needle biopsy. In addition, immediate specimen assessment by a pathologist can decrease the procedure time and the number of passes in cases of diagnostic samples, or improve the accuracy by suggesting additional samples in cases involving negative or uncertain results[12].

The size of the lesion is important for US-guided needle biopsy success. The majority of authors propose tumor size of 20 mm or greater in order to achieve a sufficiently high accuracy of percutaneous biopsies. However, a recent study performed by Kim and Chung[21], examining the accuracy of US-guided soft-tissue lesion CNB, showed that targeting lesions measuring 10 mm or more had a similar diagnostic accuracy compared to the biopsy of lesions with a length of 20 mm or greater.

The site of the lesion and its distance to the skin are mentioned as factors that can influence the needle biopsy result. Some difficult-to-assess lesions such as paraspinal tumors with deep localization are associated with a low biopsy accuracy[10]. Conversely, a recent study by Yoon *et al*.[22], examining factors contributing to the failure of US-guided core-needle MSK biopsies showed that the size, depth and location of the biopsy did not affect the diagnostic success significantly. The authors attributed their results to strict compliance with the biopsy guidelines, the uniform level of expertise among performing clinicians, and uniform biopsy technique and equipment used for all procedures.

The material should be ideally obtained from the peripheral parts of the lesion and the areas that seem to represent a higher-grade lesion on previous CT or MRI imaging because of a better chance of obtaining representative material compared to the central parts which can contain necrotic tissue[11].

Fine-needle aspiration cytology (FNAC) and core needle biopsy

Two types of imaging-guided needle biopsy are usually distinguished based on the diameter of the needle used for the procedure. FNAC is a biopsy performed with a thin, 20 Gauge or smaller diameter needle[23], used for the aspiration of lesion cells. The procedure is cost efficient, has a very low complication rate, allows an immediate assessment of biopsied material, and theoretically, carries the lowest possible risk of seeding along the biopsy track[23,24]. However, it has several limitations as well. Some authors have highlighted the low diagnostic accuracy of FNAC, especially for mesenchymal tumor grading, mostly because of inability to evaluate the lesion structure due to low quantities of biopsied material. In a study by Kasraeian *et al*.[23], evaluating the diagnostic utility of FNAC, CNB and open biopsy, the accuracy of FNAC for the diagnosis of malignancy and establishing the correct diagnosis was significantly lower compared to CNB. Therefore, FNAC is most commonly used in the evaluation of distant metastases of a known primary tumor, or confirming local tumor recurrence[24].

Still, recent reports show a high diagnostic accuracy and yield for FNAC of soft-tissue tumors, especially if an experienced physician performs the procedure in a highly specialized tertiary sarcoma center, where a multidisciplinary team can assess all aspects of the lesion and the patient, and make a decision[25]. In a metaanalysis performed by Chambers *et al*.[25] to evaluate the diagnostic performance of FNAC, the accuracy of the biopsy of MSK tumors was comparable with CNB for differentiating between benign and malignant lesions and establishing the subtype of the lesion. However, the diagnostic yield and accuracy of CNB were significantly higher for the exact diagnosis of the lesion, compared to FNAC.

CNB of MSK tumors is performed with thicker needles, with a cutting mechanism, which can acquire a sufficient amount of tissue material for the analysis of tissue structure. It is a standard diagnostic procedure in the majority of sarcoma centers, including the biopsy of mesenchymal tumors[23]. Lately, there has been a trend towards using larger diameter needles for the biopsy of soft-tissue lesions, with diameters of up to 14 G[7], since needles smaller than 18 G have a significantly lower yield[16]. Needle size, length and throw can differ depending on lesion depth and size, and operator preference. Smaller diameter needles are usually used for deeper lesions, while superficial lesion biopsies can be performed with larger, 14-gauge needles[26]. The length of throw can be bigger for larger lesions, since the specimen length of 10 mm or larger has a significantly higher diagnostic yield, compared to less than 5 mm specimens[16].

A study by Peer *et al*.[26], evaluating factors determining soft-tissue core biopsy success, showed that technical factors, such as needle diameter (14 G or 16 G) and length of the throw (9, 13, 16 or 18 mm), did not play significant role in the biopsy result, as long as strict quality of the procedures during the biopsy were respected, and proper expert analysis of viable tumor parts was performed. In addition, Wu *et al*.[19] found a similar diagnostic yield when needles with different sizes (14, 15, 16 or 18 G) were used for imaging-guided biopsies of MSK tumors. Coaxial systems, containing an introducer that can be advanced to the lesion surface, through which the core needle is inserted within the lesion and multiple passes can be obtained, can add value to the biopsy. Coaxial systems can further reduce the risk of trauma of adjacent tissues and possibly also reduce the risk of tumor track seeding[18].

Difficulties and pitfalls of core needle biopsy and possible solutions

The type of the lesion is important for the success of US-guided CNB. The CNB of certain soft-tissue lesions has a lower diagnostic success rate compared to surgical biopsy.

Cystic lesions can be sometimes difficult to be properly biopsied with imaging-guided biopsy. Kim *et al*.[21], evaluating US-guided CNB of small soft-tissue lesions, showed that predominantly cystic lesions had a significantly lower diagnostic yield compared to purely solid or predominantly solid lesions. To obtain an adequate specimen in cases of cystic lesions, a representative soft-tissue component of the lesion should be targeted. High-resolution US can be beneficial and capable of discriminating cystic from solid parts of the lesions in a high percentage of lesions.

Adipocytic and vascular soft-tissue lesions are more difficult to be properly evaluated by CNB. The reason might be the heterogeneity of these lesions, which require a large amount of material for proper evaluation of tissue architecture. Low-grade liposarcomas, for example, can contain different grade tumor cells in various regions within the same tumor[27]. A study performed by Yoon *et al*.[22], evaluating the diagnostic yield of US-guided CNB of superficial soft-tissue tumors compared to open biopsy, showed a high rate of diagnostic failure for angiosarcomas, hemangiomas, and liposarcomas.

A study evaluating the diagnostic value of US- and CT-guided MSK biopsies by Sung *et al*.[27] confirms the low diagnostic accuracy and yield for CNB of low-grade liposarcomas, vascular tumors, but also synovial sarcomas. Synovial sarcomas often have uncharacteristic cell shapes which make histological analysis more challenging[27].

Other studies have also addressed the issue of quality of CNB in mixoid tumor subtypes due to presence of inhomogeneous parts, containing either necrotic or mixoid areas, and raised the question of CNB suitability in the examination of such cases[26].

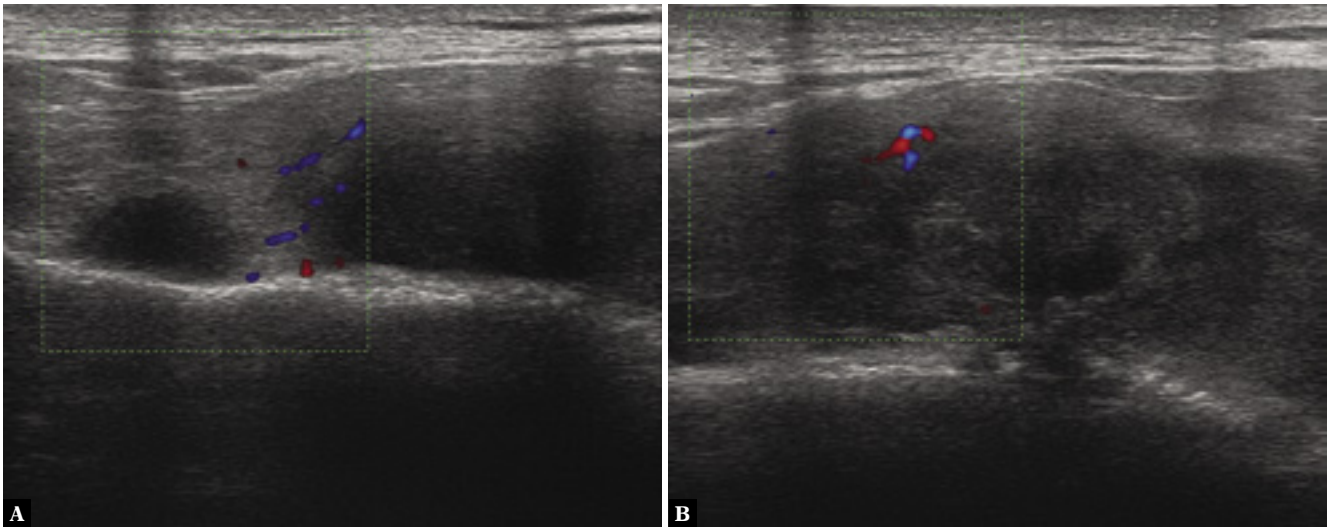

Fig. 7. *Heterogeneous, large, poorly demarcated, intramuscular soft-tissue lesion is visible. Color Doppler ultrasound is useful in discriminating between necrotic and vascularized parts, and helps to successfully target the viable part of the lesion*

Previous cross-sectional imaging can be helpful in overcoming some of these issues, and demonstrate promising biopsy sites, and has to be obtained for each soft-tissue lesion undergoing biopsy. MRI-guided biopsy with gadolinium contrast enhancement can increase the accuracy of biopsy by separating viable and necrotic tumor parts, especially in heterogeneous tumors[8].

A promising technique is US fusion imaging with cross-sectional imaging, combining the advantages of both techniques. A single study performed by Khalil *et al*.[28], including a total of 47 patients with MSK soft-tissue and bone tumors, compared the diagnostic success of fusion-guided US and CT or US and MRI core needle biopsy with CT-guided biopsy. The results showed an almost equal diagnostic yield for all evaluated techniques, with the advantage of reduced procedure and waiting time observed for the fusion-guided procedure.

Performing Doppler US prior to biopsy as part of the biopsy protocol can be advantageous in highlighting the most vascularized and viable parts of the lesion, thus helping to exclude necrotic tumor portions[26] (Fig. 7).

Contrast-enhanced ultrasound is a promising tool in soft-tissue tumor biopsy, by improving the visualization of the most viable regions of the lesion that should be targeted. It is capable of distinguishing vascularized areas of the lesion from non-vascular (necrotic) and hypovascular (possibly fibrous) parts, but also lesions which are barely or non-visible sonographically[29]. A preliminary study performed by Coran *et al*.[30], examining the role of contrast-enhanced ultrasound in CNB of soft-tissue lesions in comparison to open biopsy, concluded that the method was a promising modality for determining viable tumor parts and leading the biopsy.

Conclusion

US-guided CNB of MSK soft-tissue tumors is an accurate, less invasive (compared to open biopsy), efficient and practical procedure for obtaining adequate material for soft-tissue tumor evaluation. It should be the first-line modality for biopsy of MSK soft-tissue tumors, particularly superficial lesions accessible by US. Previous cross-sectional imaging should be performed in all cases. The strict rules of performing any biopsy should be observed, including appropriate preparation for the procedure, planning of biopsy route, which should be discussed in a multidisciplinary sarcoma conference, and targeting the best possible lesion parts. An expert physician, knowledgeable about all aspects of the biopsy procedure, and aware of possible complications, should perform the biopsy. The physician should be familiar with all advantages and possible weaknesses and limitations of the technique in different tumor types and locations, in order to achieve optimal biopsy results.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Author contributions

Original concept of study: VVN. Writing of manuscript: VVN, SI. Critical review of manuscript: SK-K, MS.

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