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Comparative cytological and histological assessment of 828 primary soft tissue and bone lesions, and proposal for a system for reporting soft tissue cytopathology

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Abstract

Introduction: The aim of the study was to evaluate the diagnostic utility of fine needle aspiration (FNA) cytology and core needle biopsies (CNBs) in a series of primary soft tissue and bone lesions and to test a possible system for reporting results of FNA cytology of soft tissue lesion.

Methods: This retrospective study encompassed 828 primary soft tissue and bone lesions, analysed with FNA, CNB and/or surgical specimen in order to perform sensitivity/specificity as well as accuracy analyses. The series was then used to test a system for reporting soft tissue cytopathology with six categories and the risk of malignancy in each category was calculated.

Results: With a malignant diagnosis defined as positive test result, FNA and CNB analysis showed sensitivity of 87% and 94%, respectively, and specificity of 89% and 95%, respectively. FNA and CNB analyses identified the correct histopathological entity of the examined lesion in 55% and 66%, respectively. The risk of malignancy within the tested categories was non-diagnostic 42%, non-neoplastic 0%, atypia of unknown significance 46%, neoplasm benign 3%, neoplasm of unknown malignant potential 27%, suspicious for malignancy 72% and malignant 97%.

Conclusion: FNA cytology is a suitable tool to determine the malignant potential of a sampled soft tissue/bone lesion but is inferior to CNB in defining the correct entity. A standardised reporting system might improve the clinical management of patients with soft tissue tumours examined primarily by FNA cytology.

KEYWORDS

biopsy, bone neoplasms, classification, core needle, fine needle, sarcoma, soft tissue neoplasms

1 | INTRODUCTION

The diagnostic process of a suspicious soft tissue or bone tumour is an interdisciplinary, multistep procedure including the clinical picture and history, radiological appearance, and morphological examination of cytological or histological material. For the practicing pathologist, the diagnosis of soft tissue and bone neoplasms often constitutes a challenge. Both soft tissue and bone tumours represent

heterogeneous groups of numerable different tumour entities. The vast majority of soft tissue and bone neoplasms are benign with an annual sarcoma incidence of 4.7/100 000, accounting for only 1% of all human malignancies.[1] Difficulties in the microscopic examinations arise due to both a morphological overlap between different benign and malignant tumour entities as well as intratumoural morphological heterogeneity.

While open biopsy has been regarded as the diagnostic gold standard, core needle biopsies (CNB) are nowadays often the first choice for morphological examination of mesenchymal neoplasms. Advantages of CNB are a retained tissue architecture, and further ancillary techniques, such as immunohistochemistry and genetic analyses, can be easily applied. Fine needle aspiration (FNA) cytology is used in many centres as a diagnostic method for recurrent disease or metastases but internationally plays only a minor role in the diagnostic process of primary soft tissue and bone neoplasms. However, Scandinavian countries have a strong tradition in FNA cytology and, at the University Hospital in Lund, Sweden, FNA cytology of soft tissue and bone tumours has been part of the primary diagnostic procedure of mesenchymal neoplasms for close to 50 years. Although acquiring less material than by CNB, FNA cytology has several advantages. The procedure is usually well tolerated without local anaesthesia and it is easy to obtain material from different regions of the lesion. Furthermore, it is a fast and cheap method, allowing on-site evaluation with subsequent directed sampling for different ancillary examinations (e.g. material for fluorescence in situ hybridisation [FISH] analysis for a suspected Ewing sarcoma). Difficulties in using FNA cytology as a primary diagnostic tool for musculoskeletal lesions arise mainly due to the heterogeneity of entities. Limited experience of soft tissue and bone cytopathology in many centres as well as a lack of a standardised and uniform reporting system for FNA cytology of soft tissue and bone lesions are further limitations of FNA cytology.

Since the 1980s, starting with Åkerman et al.,[2] a number of studies have addressed the utility of FNA cytology compared to CNB or other approaches to morphological examination of soft tissue and bone pathology. However, so far, only a few studies exist with case numbers exceeding ~100, focusing on primary mesenchymal lesions in soft tissue and bone.[3–7]

In the last decade, a standardised nomenclature and reporting system of FNA cytology for the thyroid, pancreas and salivary glands, have been published and validated.[8–10] These reporting systems provide a uniform diagnostic terminology and guidance for appropriate clinical management, to ensure optimal communication between the pathologist/cytopathologist and the clinician. Recently, cytopathologists with a special interest and expertise in soft tissue cytopathology have initiated a process to produce a sustainable approach to soft tissue FNA cytology reporting. This concept was discussed in the council meeting of the European Federation of Cytology Societies and became a project that has received support from the European Federation of Cytology Societies and the International Academy of Cytology. The steering group, which would coordinate further work to create, process and test a standardised reporting system for soft tissue cytopathology, has been formed. The group will recruit pathologists and clinicians involved in the diagnosis and treatment of patients with suspicious soft tissue lesions to process and test such a system. In the meantime, a proposal for the reporting system was presented during the European Congress of Cytology (ECC) Congress in Malmö, Sweden in June 2019. The aim of presenting this proposal was to raise discussions and follow-up efforts to form a new reporting system.

As the discussion regarding the presented proposal is not finalised and further discussion and work to reach a consensus is necessary, the material used in this study has given the authors the opportunity to test the proposed reporting system initially presented at the ECC congress in Malmö.

The primary aim of the present study was to compare the diagnostic utility of FNA and CNB in a series of 828 primary soft tissue and bone lesions. Secondly, we evaluated a proposal for a classification system for reporting soft tissue and bone cytopathology in the daily diagnostic routine.

2 | MATERIALS AND METHODS

2.1 | Patients and case selection

This retrospective study included 828 patients between 2004 and 2014 at the sarcoma centre in Lund, Sweden. The local referral guidelines recommend that all subcutaneous lesions larger than 5 cm and all deep-seated soft tissue lesions are examined at a sarcoma centre. The study encompassed patients that were (1) referred for tissue sampling from the Department of Orthopedic Surgery because of a suspected soft tissue or bone tumour and (2) from whom both FNA and at least one histological sample (CNB, open biopsy, surgical resection specimen) were available for analysis. FNA and CNB of palpable tumour masses in both soft tissue and bone were performed at the FNA clinic of the Department of Pathology without assistance of ultrasound or radiological imaging. Non-palpable masses were sampled at the Department of Radiology with ultrasound or CT guidance, occasionally with on-site evaluation of the obtained material by a cytopathologist. The study encompassed only primary mesenchymal lesions.

Of the 828 included patients, 369 (45%) were female and 459 (55%) were male. FNA, CNB and surgical specimens (open biopsy or resection specimens after surgical treatment) were available in 349 (42%) cases, FNA and a surgical specimen in 322 (39%) cases, and FNA and CNB specimens in 157 (19%) cases. When available, a surgical specimen was considered the diagnostic gold standard; in the 157 cases without such material, the FNA diagnosis in combination with clinical follow-up was used to define the malignant potential of a lesion (used for sensitivity/specificity analyses only).

For a detailed summary of the clinicopathological data, see Table 1.

TABLE 1 Epidemiological and clinicopathological data

Epidemiological/clinicopathological data	Number of cases (% of total)
Cases total	828 (100)
Sex	
Female	369 (45)
Male	459 (55)
Age 1-94 y (median 53)	
Soft tissue tumours	
Total	732 (88)
Benign	480 (58)
Malignant	250 (30)
UMP	2 (0.2)
Bone tumours	
Total	96 (12)
Benign	31 (4)
Malignant	65 (8)
Topography	
Trunk	134 (16)
Limb proximal	457 (55)
Limb distal	199 (24)
Head/neck	36 (4)
Abdomen/retroperitoneum	2 (0.2)

Abbreviation: UMP, unknown malignant potential.

2.2 | Cytological specimens

Fine-needle aspiration was performed with 22-24 gauge needles and 10-mL disposable syringes using a Cameco syringe holder (Cameco AB). Between two and six punctures were performed per case. Cytological smears were either air-dried and stained with May-Grünwald Giemsa (Giemsa) or fixated in 96% ethanol and stained with haematoxylin-eosin (HE). For cell-block (CB) preparation the needles were rinsed with CytoLyt solution (Hologic, ThinPrep, Stockholm, Hologic, Inc) with subsequent automated CB preparation (Hologic, Cellient Automated Cell Block System), according to the manufacturer's instructions. CB was used for routine HE stains and immunohistochemical stains, both optimised for formalin-fixed paraffin-embedded tissue samples. Alternatively, immunocytological stains were performed on liquid-based cytological specimens (ThinPrep). CB were prepared in 231 (28%) cases. Immunohisto/cytological analyses were performed in 58 (7%) of the FNA and CB cases.

2.3 | Histological specimens

Three to six CNB were performed on each lesion. CNB, open biopsies and resection specimens were fixed in 4% buffered formaldehyde for 12-24 hours and the tissue samples were subsequently embedded in paraffin. After sectioning, HE and immunohistochemical stains were carried out following routine protocols. Immunohistochemical stains were performed on 267 (53%) CNB and 245 (36%) surgical specimens.

2.4 | Genetic analyses

Various genetic analyses, mostly chromosome banding or FISH, were performed on a minority of cases—34 (4%) FNA/CB, 22 (4%) CNB, 301 (45%)—surgical specimens. All FISH analyses were performed using commercial locus-specific probes for the *EWSR1*, *FUS*, *MDM2* or *SS18* loci; the manufacturers varied during the study period.

2.5 | Case clustering for sensitivity/specificity analyses

For sensitivity and specificity analyses, every diagnosis on FNA/CB, CNB and surgical material was assigned to one of the following diagnostic groups: (1) insufficient material, (2) inconclusive, (3) benign and (4) malignant/suspected malignant. A malignant diagnosis was considered a positive test result, a benign diagnosis was considered a negative test result. Insufficient material meant that no diagnostic material could be obtained or that technical issues or artefacts made proper analysis impossible. An inconclusive FNA or CNB result meant that it could not be defined whether a lesion was benign or (suspected) malignant. Cases providing an inconclusive diagnosis were treated as false diagnosis for the sensitivity/specificity analyses. Cases with insufficient material as well as cases where the malignant potential of a lesion remained unclear even after analysis of surgical material (two cases) were excluded from the sensitivity/specificity analyses.

For the calculations of the diagnostic accuracy, all FNA and CNB analyses with sufficient material and surgical follow-up were included (FNA n = 639, CNB n = 320). The two cases with unknown malignant potential even after analysis of the resection specimens were excluded. A diagnosis was regarded as accurate when it matched the final diagnosis. As an example, a FNA diagnosis of lipoma and a resection specimen diagnosis of angiolipoma was regarded as not matching.

2.6 | Case clustering for a suitable system for reporting soft tissue cytopathology

In a second step, we attempted to test a suitable reporting system for soft tissue cytopathology. Due to the marked heterogeneity within musculoskeletal tumours, only soft tissue lesions and not bone lesions were included in the analysis. The proposed reporting system closely follows the example of the Milan System for Reporting Salivary Gland Cytopathology[4] in order to manage a variety of different reactive, benign and malignant conditions.

TABLE 2 Histological entities[a]

Diagnosis	Total number	Number of cases correctly diagnosed as benign or malignant [b]		Number of cases with accurate histological diagnosis [c]	
		FNA	CNB	FNA	CNB
Alveolar soft part sarcoma	2	$2^{/2}$	$1^{/1}$	$1^{/1}$	–
Aneurysmal bone cyst	6	$5^{/6}$	$1^{/1}$	$2^{/5}$	–
Angioleiomyoma	2	$2^{/2}$	$1^{/1}$	$0^{/1}$	–
Angiolipoma	10	$10^{/10}$	–	$3^{/10}$	–
Angiosarcoma	1	$1^{/1}$	$1^{/1}$	–	–
Arteriovenous malformation	1	$1^{/1}$	–	$0^{/1}$	–
Atypical lipomatous tumour	17	$11^{/15}$	$9^{/9}$	$9^{/13}$	$7^{/7}$
Benign fatty tissue	1	$1^{/1}$	–	$0^{/1}$	–
Benign mesenchymal proliferation	4	$3^{/4}$	$4^{/4}$	–	–
Chrondroblastoma	1	$0^{/1}$	–	$0^{/1}$	–
Chondroid syringoma	1	$1^{/1}$	$1^{/1}$	$1^{/1}$	$1^{/1}$
Chondroma, soft tissue	1	$1^{/1}$	$1^{/1}$	$1^{/1}$	$1^{/1}$
Chondromyxoid fibroma	3	$3^{/3}$	$1^{/1}$	$2^{/3}$	$1^{/1}$
Chondrosarcoma conventional	30	$24^{/29}$	$15^{/18}$	$21^{/26}$	$12^{/15}$
Chondrosarcoma, clear cell	1	$0^{/1}$	–	$0^{/1}$	–
Chondrosarcoma, dedifferentiated	1	$0^{/1}$	$0^{/1}$	$0^{/1}$	$0^{/1}$
Desmoplastic fibroblastoma	3	$2^{/2}$	$3^{/3}$	$0^{/1}$	$0^{/2}$
Dermatofibrosarcoma protuberans	13	$7^{/13}$	$11^{/11}$	$5^{/12}$	$10^{/10}$
Elastofibroma dorsi	5	$5^{/5}$	$5^{/5}$	–	–
Enchondroma	3	$3^{/3}$	–	$2^{/3}$	–
Epithelioid hemangioendothelioma	1	$0^{/1}$	–	$0^{/1}$	–
Epithelioid sarcoma	1	$0^{/1}$	–	$0^{/1}$	–
Ewing sarcoma	6 Soft tissue, 6 bone	$12^{/12}$	$11^{/11}$	$5^{/8}$	$7^{/7}$
Extraskeletal myxoid chondrosarcoma	1	$0^{/1}$	–	$0^{/1}$	–
Fibroma, nuchal	1	$1^{/1}$	$1^{/1}$	$0^{/1}$	$0^{/1}$
Fibroma of tendon sheath	1	$1^{/1}$	–	$0^{/1}$	–
Fibromatosis, desmoid	27	$23^{/27}$	$26^{/27}$	$4^{/8}$	$7^{/8}$
Fibromatosis, palmar	1	$0^{/1}$	–	$0^{/1}$	–
Fibromatosis, plantar	5	$5^{/5}$	$1^{/1}$	$5^{/5}$	$1^{/1}$
Fibrous dysplasia	1	–	$1^{/1}$	–	–
Fibrous hamartoma of infancy	1	$1^{/1}$	–	$0^{/1}$	–
Fibrous histiocytoma	4	$2^{/3}$	$2^{/3}$	$1^{/3}$	$2^{/3}$
Gastrointestinal stromal tumour	1	–	$1^{/1}$	–	$1^{/1}$
Giant cell reparative granuloma	1	$0^{/1}$	–	$0^{/1}$	–
Giant cell tumour of bone	12	$10^{/11}$	$4^{/4}$	$9^{/11}$	$4^{/4}$
Granular cell tumour, benign	2	$2^{/2}$	$1^{/1}$	$2^{/2}$	$1^{/1}$
Haemangioma	29	$21^{/25}$	$8^{/8}$	$14^{/21}$	$3^{/3}$
Haemosiderotic fibrolipomatous tumour	1	$0^{/1}$	$1^{/1}$	$0^{/1}$	$0^{/1}$
Hibernoma	3	$3^{/3}$	$2^{/2}$	$2^{/3}$	$2^{/2}$
Langerhans cell histiocytosis	2	$2^{/2}$	$2^{/2}$	$2^{/2}$	$2^{/2}$
Leiomyoma	2	$2^{/2}$	–	$0^{/2}$	–
Leiomyosarcoma	35	$30^{/33}$	$28^{/28}$	$5^{/31}$	$14^{/26}$

(Continues)

TABLE 2 (Continued)

Diagnosis	Total number	Number of cases correctly diagnosed as benign or malignant [b]		Number of cases with accurate histological diagnosis [c]	
		FNA	CNB	FNA	CNB
Lipoblastoma	1	$1^{/1}$	–	$0^{/1}$	–
Lipoma	172	$166^{/172}$	$30^{/31}$	$138^{/155}$	$11^{/14}$
Lipoma, spindle cell	18	$14^{/18}$	$11^{/11}$	$3^{/13}$	$5^{/6}$
Liposarcoma, dedifferentiated	6	$6^{/6}$	$4^{/4}$	$3^{/6}$	$2^{/4}$
Liposarcoma, myxoid	12	$11^{/12}$	$11^{/11}$	$6^{/10}$	$8^{/9}$
Liposarcoma, pleomorphic	7	$6^{/6}$	$4^{/4}$	$1^{/6}$	$3^{/4}$
Low-grade fibromyxoid sarcoma	3	$1^{/3}$	$0^{/2}$	$0^{/3}$	$0^{/2}$
Low-grade myofibroblastic sarcoma	2	$1^{/2}$	$2^{/2}$	$0^{/2}$	$0^{/2}$
Malignant peripheral nerve sheath tumour	9	$4^{/6}$	$8^{/8}$	$0^{/6}$	$2^{/8}$
Myxofibrosarcoma	37	$35^{/37}$	$24^{/26}$	$13^{/35}$	$11^{/25}$
Myxoid spindle cell tumour UMP	2	NA	NA	NA	NA
Myxoinflammatory fibroblastic sarcoma	1	$1^{/1}$	$1^{/1}$	$0^{/1}$	$1^{/1}$
Myxoma	16	$11^{/15}$	$9^{/12}$	$7^{/11}$	$4^{/8}$
Neurofibroma	14	$10^{/13}$	$9^{/10}$	$5^{/10}$	$5^{/7}$
Nodular fasciitis	6	$5^{/6}$	$6^{/6}$	$1^{/3}$	$1^{/3}$
Osteochondroma	1	$1^{/1}$	$1^{/1}$	–	–
Osteosarcoma, conventional	24	$19^{/21}$	$15^{/18}$	$10^{/20}$	$11^{/17}$
Osteosarcoma, parosteal	1	$1^{/1}$	$1^{/1}$	$1^{/1}$	$1^{/1}$
Perineurioma	2	$1^{/2}$	$0^{/1}$	$0^{/2}$	$0^{/1}$
Plexiform fibrohistiocytic tumour	1	$0^{/1}$	$1^{/1}$	$0^{/1}$	$0^{/1}$
Reactive	63	$57^{/63}$	$52^{/53}$	$13^{/19}$	$8^{/9}$
Rhabdomyosarcoma, alveolar	1	$1^{/1}$	$1^{/1}$	–	–
Rhabdomyosarcoma, pleomorphic	1	$1^{/1}$	$1^{/1}$	$0^{/1}$	$0^{/1}$
Rhabdomyosarcoma, spindle cell	1	$1^{/1}$	$1^{/1}$	–	–
Schwannoma	54	$45^{/51}$	$24^{/25}$	$34^{/43}$	$16^{/17}$
Solitary fibrous tumour	7	$2^{/7}$	$6^{/7}$	$0^{/6}$	$4^{/6}$
Solitary fibrous tumour, malignant	4	$0^{/4}$	$2^{/3}$	$0^{/3}$	$1^{/2}$
Spindle cell sarcoma NOS	18	$15^{/17}$	$17^{/18}$	$0^{/9}$	$0^{/9}$
Superficial angiomyxoma	1	$1^{/1}$	$1^{/1}$	–	–
Synovial chondromatosis	2	$1^{/2}$	$0^{/1}$	$0^{/2}$	$0^{/1}$
Synovial sarcoma	14	$13^{/14}$	$10^{/10}$	$9^{/13}$	$8^{/9}$
Tenosynovial giant cell tumour	19	$17^{/17}$	$5^{/5}$	$13^{/15}$	$3^{/3}$
Undifferentiated pleomorphic sarcoma	57	$56^{/56}$	$51^{/51}$	$0^{/51}$	$30^{/46}$
Venous malformation	1	–	$1^{/1}$	–	$0^{/1}$

Abbreviations: CNB, Core needle biopsy; FNA, Fine-needle aspiration; NA, not applicable; NOS, not otherwise specified; UMP, unknown malignant potential.

[a] Diagnoses in italics = bone lesions.

[b] Superscript indicating number of cases that were included in the analysis. Cases with insufficient material were excluded.

[c] Superscript indicating number of cases that were included in the analysis. Cases with insufficient material as well as cases without surgical follow-up were excluded.

The classification system that was tested included six categories with their respective risk of malignancy, similar to established reporting systems. Samples were designed as non-diagnostic (I) when the quality or quantity of the diagnostic material was insufficient for evaluation. Furthermore, inadequate specimen with discrepancy in the triple test between the cytomorphological, clinical and radiology diagnosis was included in this category. Specimen adequacy in soft tissue FNA has not yet been clearly defined. A minimal absolute

number of cells in FNA specimen can be difficult to estimate, due to the heterogeneity of the conditions. FNA cytology samples of specific entities often show low cellularity (ganglion, vascular lesions) and even a small number of atypical cells can raise suspicion for malignancy.

The non-neoplastic category (II) included a variety of non-neoplastic conditions covering haematomas, inflammatory conditions of various kinds, proliferative myositis and fasciitis, ganglion cysts, synovial cysts, gout, and endometriosis. The presence of cystic changes, histiocytes, necrosis, inflammatory cells and granulomatous reactions can be misleading, as some high-grade sarcomas are associated with necrosis and occasionally foreign body granulomatous reactions. The clinico-radiological correlation is again essential to ensure that the obtained material is representative of the lesion.

The category atypia of unknown significance (III) included cases that, based on the cytomorphology, did not fulfill the criteria for a neoplasm but where a neoplasm could not be excluded.

The neoplastic categories were divided into four groups: benign neoplasms (IVa), neoplasms of undetermined malignant potential (IVb), neoplasms with suspicion for malignancy (V) and malignant neoplasms (VI).

Category IVa included cases where cytomorphological analysis led to a specific histological diagnosis according to established diagnostic criteria, i.e. various benign lipomatous tumours, benign nerve sheath tumours and tenosynovial giant cell tumours. Furthermore, we believe that this category should include low cellularity specimens or specimens with preparation artefacts that were suggestive of a benign neoplasm, without being able to define the specific entity of the condition. IVb was an intermediate category for neoplasms that could not be reliably classified as benign or malignant based on the cytomorphological picture. Part of this entity consisted of malignant neoplasms with sparse material, spindle cell and myxoid neoplasms or rare entities with poorly defined cytological criteria. Category V covered cases with cytomorphological features that raised suspicion but were not unequivocal for malignancy. This feature separated category V from category IV; in the latter two categories, attempts were made to provide differential diagnoses.

The risk of malignancy within a given category was calculated as the number of malignant cases at final histological diagnoses divided by the total number of cases in the respective category.

2.7 | Statistical evaluation

Statistical evaluation covered frequency analyses, which subsequently were used for sensitivity, specificity and accuracy calculations. The analyses were carried out with SPSS version 25 (IBM).

3 | RESULTS

3.1 | Clinicopathological data

For a detailed view of the clinicopathological data see Table 1.

The follow-up time varied depending on the type of lesion and potential complications after treatment. In general, patients with benign lesions were not actively followed, but they were instructed to contact the hospital in case of recurrent problems. The follow-up time varied between 0 and 171 months (mean 57 months). Stratified for benign and malignant conditions, the follow-up time ranged from 0 to 156 months (mean 45 months) for benign and 1 to 171 months (mean 62 months) for malignant lesions.

At the end of the observation time, a total of 179 patients had died. Of those patients, 47 had benign soft tissue or bone lesions; the death of 10 of these patients was caused by other malignancies, and no information about the cause of death was available in seven cases. None of the deaths in the remaining cases were linked to the examined soft tissue or bone condition. In the group of patients with malignant soft tissue or bone tumours, 131 were dead at the end of the observation time, mostly related to the examined disease. No information about the cause of death within this group was available for 22 patients, and 15 patients died of other causes than the examined soft tissue or bone tumour, including a different malignancy in one case.

In two cases, it was uncertain even after the examination of the resection specimen whether the final diagnosis was benign or malignant. One of those cases was an 86-year-old patient with a 7-cm mass in the thigh. On FNA material, a low-grade myxofibrosarcoma was suspected, while on CNB material, the differential diagnoses covered low-grade myxofibrosarcoma and myxoid liposarcoma. The case remained unclear after resection with low-grade myxofibrosarcoma, myxoinflammatory fibroblastic sarcoma and myxoma as potential diagnoses. The patient died 4 years after surgical treatment without signs of relapse. The other case was a 64-year-old male with a 3-cm soft tissue mass in the foot. FNA analysis revealed a spindle cell neoplasm of unknown malignant potential and on CNB a haemangioma was suspected. The resection specimen showed a myxoid spindle cell neoplasm with only discrete atypia and unknown malignant potential. Six years after the resection, the patient was alive without signs of recurrence or metastases.

No clinical data were available for 20 patients.

All final diagnoses are summarised in Table 2 along with the absolute number of each entity in the second column.

3.2 | Diagnostic utility of FNA cytopathology compared to core needle biopsies (CNB)—sensitivity/specificity and accuracy analyses

The classes of diagnostic results of FNA and CNB analysis showed a different distribution and are listed in Table 3. Insufficient material by FNA was obtained in 31/828 (4%) samples and by CNB in 27/506 (5%) of samples. In contrast, the number of inconclusive results was (both absolutely and relatively) higher in FNA compared to CNB samples (67/828 [8%] vs 14/506 [3%] cases).

FNA analysis led to 15 false-positive (FP; 2%) and 12 false-negative (FN; 1%) diagnoses, whereas CNB yielded six FP and six FN

(1% and 1%, respectively). The diagnostic errors in FNA and CNB material led to false diagnoses prior to treatment in seven of the FP and in nine of the FN analyses. All FP and FN results are summarised in Table 4. The majority of these results originated from two groups of tumours. The first group encompassed lipomatous tumours with the differential diagnosis between lipoma and atypical lipomatous tumour (ALT), accounting for four of the FN and six of the FP cases. The second group encompassed spindle cell tumours with no or low-grade atypia, accounting for seven of the FN and eight of the FP cases. The sensitivity and specificity of FNA and CNB analyses are summarised in Table 5. Note that FNA and CNB results unable to differentiate between benign and malignant conditions were treated as FP/FN for sensitivity/specificity analyses but are not shown in Table 5 as those cases did not result in real FP/FN diagnoses.

Of the 639 FNA analyses, that were included in the accuracy analysis, 353 (55%) analyses defined the correct histological entity of the sampled lesion. Of all FNA analyses that resulted in a specific histological diagnosis, 88% were correct. Accordingly, of the 320 CNB analyses, included in the accuracy analysis, 211 (66%) defined correctly the sampled entity. This accounts for 90% of all CNB analyses, providing a specific histological diagnosis.

3.3 | Proposal system for reporting soft tissue cytopathology

Results of the frequency analyses and risk for malignancy in the different categories are summarised in Table 6.

In the current study, there was a 42% risk for malignancy in category I (n = 24). CNBs were performed in all but two cases. Four CNB specimens likewise showed insufficient material. The final diagnoses in this sampling error category covered various benign and malignant entities with nerve sheath tumours (three schwannomas, one neurofibroma, three malignant peripheral nerve sheath tumours [MPNSTs]) as the largest group.

Category II showed no risk for malignancy, with all 66 cases being benign. However, the final diagnoses of the cases in this category did not exclusively show non-neoplastic conditions, but also 11 benign tumours: five haemangiomas, two desmoid fibromatoses and one each of lipoma, hibernoma, fibroma of tendon sheath and elastofibroma dorsi. The two cases with potentially therapeutic consequences (desmoid fibromatosis) were correctly diagnosed on CNB material.

Category III encompassed 11 cases, five (46%) of those turned out to be malignant. Those malignant conditions included two high-grade spindle cell sarcomas not otherwise specified, one low-grade fibromyxoid sarcoma (LGFMS), one malignant solitary fibrous tumour and one high-grade leiomyosarcoma. The LGFMS showed an unclear myofibroblastic proliferation on FNA material. The FNA specimens of the four remaining sarcomas in this category were scanty with some atypical cells. The benign conditions included four cases with unspecific reactive changes, one desmoid fibromatosis and one hemangioma.

Category IVa included 339 cases, of which 329 (97%) were correctly diagnosed as benign. The risk of malignancy was 3%. Nine malignant neoplasms were falsely diagnosed as benign neoplasms. In four of those FN cases, a correct diagnosis was set prior to treatment on material from CNB or open biopsies. The FN cases are summarised in Table 4. All cases correctly diagnosed as benign conditions were neoplasms; consequently, there were no non-neoplastic conditions in this category. Furthermore, one of the lesions with unknown malignant potential after surgical treatment was diagnosed as haemangioma on FNA material and fell into category IVa.

Seventy cases were assigned to the intermediate category IVb with a risk for malignancy of 27%. FNA cytology specimens in this category mainly showed spindle cell lesions with no or low-grade atypia. Twenty-five cases were reported as spindle cell neoplasm of unknown malignant potential (13 of those cases were malignant tumours). Thirteen cases showed cytologically myxoid spindle cell tumours of unknown malignant potential (five of those cases were malignant tumours in the end). Other groups of FNA diagnoses included lipomatous tumours as well as suspected vascular or nerve sheath tumours with unknown malignant potential. Finally benign cases included nine schwannomas, five neurofibromas, one perineurioma, six spindle cell lipomas, three lipomas, four desmoid fibromatoses, one palmar fibromatosis, three intramuscular myxomas, four benign solitary fibrous tumours, two tenosynovial giant cell tumours (diffuse type), one synovial chondromatosis, two nodular fasciitis, two desmoplastic fibroblastomas, three haemangiomas, one haemosiderotic fibrolipomatous tumour, one elastofibroma dorsi and two benign mesenchymal proliferations not otherwise specified. The malignant tumours covered six dermatofibrosarcoma protuberans (DFSP), three malignant solitary fibrous tumours, three high-grade leiomyosarcomas, and one each of extraskeletal myxoid chondrosarcoma, epithelioid hemangioendothelioma, myxoid liposarcoma, LGFMS, low-grade myofibroblastic sarcoma, high-grade MPNST and myxofibrosarcoma. Only one lesion was of non-neoplastic nature (gout).

Category V included 32 cases with a risk of malignancy of 72%. One part of the FNA specimens within this category raised general suspicion for a spindle cell or myxoid sarcoma (14 and four cases, respectively), in one case suspicion for a pleomorphic sarcoma. Another part of the FNA results raised suspicion for a special tumour entity, most commonly myxoid liposarcoma or low-grade chondrosarcoma (four cases each), suspicion for ALT (two cases), and one case each suspicion for DFSP, MPNST, synovial sarcoma and alveolar soft part sarcoma. All cases within this category were finally diagnosed as neoplasms after histological examination. The malignant diagnoses covered a variety of different tumour entities with the most common being undifferentiated pleomorphic sarcomas, myxoid liposarcomas and myxofibrosarcomas. However, there were nine benign neoplasms, where a malignant tumour was suspected on FNA cytology. These FP cases are summarised in Table 4. Three suspected ALT, two suspected spindle cell sarcomas and one suspected LGFMS were diagnosed on CNB material as lipoma/pleomorphic lipoma,

TABLE 3 Diagnostic results

Material (total n)	Diagnostic results	Total n (% of total)	Final diagnosis benign n (% of total)	Final diagnosis malignant n (% of total)	Final diagnosis with UMP n (% of total)
FNA/CB (n = 828)	Insufficient material	31 (4)	16 (2)	15 (2)	—
	Inconclusive	67 (8)	38 (5)	29 (4)	—
	Benign	455 (55)	442 (53)	12 (1)[b]	1 (0.1)
	(Suspected) Malignant	275 (33)	15 (2)[a]	259 (31)	1 (0.1)
CNB (n = 506)	Insufficient material	27 (5)	9 (2)	18 (4)	—
	Inconclusive	14 (3)	6 (1)	8 (2)	—
	Benign	228 (45)	221 (44)	6 (1)[b]	1 (0.2)
	(Suspected) Malignant	237 (47)	6 (1)[a]	230 (45)	1 (0.2)
Surgical material[c] (n = 671)	Insufficient material	0	0	0	0
	Inconclusive	2 (0.3)	0	0	2 (0.3)
	Benign	385 (57)	385 (57)	0	0
	(Suspected) Malignant	284 (42)	0	284 (42)	0

Abbreviations: CB, cell block; CNB, core needle biopsy; FNA, fine needle aspiration cytology; UMP, unknown malignant potential.

[a]False-positive cases, for details see Table 4.

[b]False-negative cases, for details see Table 4.

[c]Surgical biopsies and resections.

ischaemic fasciitis, solitary fibrous tumour and myxoma, respectively. One suspected spindle cell sarcoma, one suspected MPNST and one suspected DFSP on FNA were misinterpreted also on CNB material, leading to a wrong diagnosis prior to treatment.

Category VI in this study encompassed 190 cases with a risk of malignancy of 97%. The final diagnoses covered a variety of malignant soft tissue and bone tumour entities with undifferentiated pleomorphic sarcomas, myxofibrosarcomas, leiomyosarcomas, synovial sarcomas and ALT being the most common. The malignant potential of one case (FNA cytology myxofibrosarcoma) remained unclear even after surgical resection (differential diagnosis between myxoinflammatory fibroblastic sarcoma, low-grade myxofibrosarcoma or myxoma). Category VI covered five FP cases, listed in Table 4. Four false FNA diagnoses (two ALT and two carcinoma metastases) were corrected by CNB analysis. In the remaining FP case, both FNA and CNB failed in identifying a desmoid fibromatosis that was mistaken as a low-grade sarcoma. This case was the only one within this category causing a wrong diagnosis prior to treatment.

4 | DISCUSSION

FNA and CNB have become popular diagnostic tools in the diagnostic process of soft tissue and bone lesions because they can be performed in an outpatient setting and carry low risk of morbidity. However, FNA in many facilities is mostly used for the diagnosis of recurrent or metastatic disease. The current study was based on a series of 828 patients with primary soft tissue and bone lesions, admitted to the sarcoma centre of the University Hospital in Lund/Sweden (Department of Orthopedic Surgery). As paediatric patients and patients with abdominal/retroperitoneal lesions are treated by paediatricians and visceral surgeons, respectively, those groups were underrepresented in the study.

Open incisional and excisional biopsy is generally accepted sampling techniques in the diagnosis of musculoskeletal neoplasms. The open biopsy usually provides sufficient tissue for histopathological examination as well as for ancillary studies. The reported diagnostic accuracy of open biopsy lies around 88%-100%.[11–13] However, open biopsy requires general anaesthesia and there are risks of intraoperative and postoperative complications, such as haematoma, infection and wound dehiscence. In addition, a poorly placed incisional biopsy can break the natural barriers for tumour growth, which can increase the risk of tumour contamination into surrounding tissues. Overall, an open biopsy procedure has a reported complication rate of 12%-17%.[14]

Our results revealed a general FNA sensitivity and specificity of 87% and 89%, respectively. With regard to general parameters such as a malignant vs benign test results, previous studies have shown a wide range (65%-100%) of correct FNA analyses.[15] Possible reasons for the wide range of those analyses are difficult to evaluate but might include differences in diagnostic experience, inclusion of cases of recurrent disease (and thus already known tumour entities), as well as differential use of ancillary techniques (cell block, immunocytochemistry, genetic analyses). In addition, it has to be considered that the case collection in many studies was rather heterogeneous with primary soft tissue/bone lesions along with metastatic carcinomas, melanomas and haematopoietic malignancies.[13,16–19] Only a few studies were mainly focused on primary soft tissue/bone lesions and had case numbers exceeding 200 examined cases.[6,7]

A comparable issue concerns the accuracy of analyses, here defined as identifying the correct entity of the sampled lesion. We found that 88% of all FNA diagnoses, revealing a specific histological

TABLE 4 False-negative (FN) and false-positive (FP) cases in fine needle aspiration (FNA) and core needle biopsy (CNB) specimen

Case ID	Sex/age (y)	Location/ size (cm)	FNA diagnosis	CNB diagnosis	SB diagnosis	Resection specimen diagnosis	Correct pre-treatment diagnosis
False-negative cases (FN diagnosis bold)							
38[a]	F/18	Knee/ 7	**Possibly tenosynovial giant cell tumour**	**Probably tenosynovial giant cell tumour**	—	Plexiform fibrohistiocytic tumour	No
42	F/53	Neck/ 10	Myxoid spindle cell tumour, unknown type	**SFT**	—	Malignant SFT	No
553[a]	F/27	Upper arm/ 4	**Spindle cell neoplasm, possibly schwannoma**	—	—	Synovial sarcoma	No
590	M/17	Lower leg/ 5	**Benign chondroid tissue**	**Benign chondroid tumour**	—	Osteosarcoma	No
594	F/25	Pelvis/NA	Sparse material, suspicious for malignancy	**Benign chondroid tumour**	Chondroblastic Osteosarcoma	—	—
596	M/27	Pelvis/ 7	Cartilage tumour, unknown type	**Cartilage tumour, favoring osteochondroma**	—	Chondrosarcoma	No
607[a]	F/54	Abdominal wall/ 5	**Neurofibroma with atypia**	Probably MPNST	—	MPNST	Yes
608[a]	F/56	Thigh/ 4	**Lipoma**	—	—	ALT	No
651[a]	M/62	Upper arm/ 16	**Lipoma**	—	—	ALT	No
746[a]	F/65	Knee/ 3	**Schwannoma**	Low-grade malignant spindle cell tumour	—	Low-grade myxofibrosarcoma	Yes
755[a]	F/49	Lower arm/ 10	**Lipoma**	—	—	ALT	No
758	M/41	Proximal femur/NA	**Skeletal tumour, probably benign**	—	Clear cell chondrosarcoma	Clear cell chondrosarcoma	Yes
779[a]	M/71	Thorax, NA	**Lipoma**	—	—	ALT	No
819[a]	F/16	Pelvis/ NA	**ABC or GCT**	**ABC or GCT**	Osteosarcoma	Osteosarcoma	Yes
820	F/14	Thoracic wall/ 1.5	**Benign spindle cell tumour**	—	—	Epithelioid sarcoma	No
False-positive cases (FP diagnosis bold)							
16[b]	M/60	Thoracal wall/ 18	**ALT**	Lipoma	—	—	—
24[b]	M/44	Axilla/ 10	**ALT**	Lipoma	—	Lipoma	Yes
60[c]	M/57	Upper Arm/ 20	**Suspicious for ALT**	Lipoma	—	Lipoma	Yes
133[c]	M/72	Neck/ 9	**Suspicious for ALT**	Pleomorphic lipoma			—
137[b]	F/66	Thorax wall/ 5	**Low-grade sarcoma**	**Low-grade sarcoma**	—	Desmoid	No

(Continues)

TABLE 4 (Continued)

Case ID	Sex/age (y)	Location/ size (cm)	FNA diagnosis	CNB diagnosis	SB diagnosis	Resection specimen diagnosis	Correct pre-treatment diagnosis
142[c]	M/62	Thorax wall/ 8	**Spindle cell tumour, suspicious for haemangioendothelioma**	—	—	Haemangioma	No
184[c]	M/62	Thigh/ 20	**Suspicious for ALT**	Lipoma	—	Lipoma	Yes
195[c]	F/55	Lower leg/NA	**Suspicious for MPNST**	**Atypical neurofibroma, MPNST not ruled out**	—	Neurofibroma	No
233[b]	M/69	Groin/ 5	**Carcinoma metastasis**	SFT	—	SFT	Yes
308[c]	M/46	Thigh/5	**Suspicious for LGFMS**	Myxoma		Myxoma	Yes
338[c]	M/15	Trunk/2	**Suspicious for DFSP**	**DFSP**	—	Fibrous histiocytoma	No
365[b]	F/51	Femur/NA	**Carcinoma metastasis**	Reactive	—	Reactive/ callus	Yes
405[c]	F/88	Gluteal region/ NA	**Suspicious for sarcoma**	Ischemic fasciitis	—	—	—
505	F/28	Lower arm/ 6	Spindle cell neoplasm, unknown type	**Suspicious for low-grade fibromyxoid sarcoma**	—	Perineurioma	No
518	M/47	Shoulder/ 5	Lipomatous tumour, unknown type	**ALT**	—	Lipoma	No
519	M/22	Foot/ NA	**Suspicious for low-grade chondrosarcoma**	**Most likely low-grade chondrosarcoma**	—	Synovial chondromatosis	No
802[c]	M/73	Lower leg/ 10	**Suspicious for sarcoma**	SFT	—	SFT	Yes

Abbreviations: ABC, aneurysmal bone cyst; ALT, atypical lipomatous tumour; ALT, atypical lipomatous tumour; CNB, core needle biopsy; F, female; FNA, fine-needle aspiration; GCT, giant cell tumour; LGFMS, low-grade fibromyxoid sarcoma; M, male; MPNST, malignant peripheral nerve sheath tumour; MPNST, malignant peripheral nerve sheath tumour; MPNST, malignant peripheral nerve sheath tumour; NA, not available; SB, surgical biopsy; SFT, solitary fibrous tumour; SFT, solitary fibrous tumour.

[a] False-negative cases in FNA classification group IVa (benign neoplasms).

[b] False-positive cases in FNA classification group VI (malignant).

[c] False-positive cases in FNA classification group V (suspicious for malignancy).

TABLE 5 Sensitivity/specificity of FNA and CNB analysis

	Sensitivity	Specificity
Total		
FNA (n = 794)	87	89
CNB (n = 475)	94	95
Soft tissue lesions		
FNA (n = 705)	87	90
CNB (n = 422)	96	95
Bone lesions		
FNA (n = 89)	85	83
CNB (n = 53)	86	91

Abbreviations: FNA, fine needle aspiration; CNB, core needle biopsy.

diagnosis, were correct, accounting for the results of 55% of all FNA analyses with surgical follow-up. Previous studies showed a wide range of accuracy between 33%-93%.[6,7,13,20,21] The reasons for that wide range might be comparable to those considered above in the context of sensitivity/specificity analyses. In addition, it was not always clear if the reported results in previous studies concerning the diagnostic accuracy of FNA analyses were based only on cases, where a specific histological diagnosis was reported or on the total number of analysed FNA cases.

The summary of FP and FN diagnoses (Table 4) as well as the summary of all reported diagnoses in this study (Table 2) mirror that certain groups of tumours are more problematic than others when it comes to determining the malignant potential or to make an accurate histopathological diagnosis. One of those tumour groups is spindle cell lesions with no or low-grade atypia. In the current study these were benign nerve sheath tumours, fibrous histiocytomas and myxomas vs sarcomas with low-grade cytomorphological features such as low-grade MPNST, synovial sarcomas, low-grade myxofibrosarcomas and LGFMS. Diagnostic pitfalls are based on morphological overlap between the different tumour entities and their morphological variations, as described before.[22–25] Another problematic group encompassed lipomas and ALT. In absence of lipoblasts or atypical spindle cells in FNA specimen, it is not possible to morphologically differentiate between those tumourous entities. Regressive changes and histiocytic reactions can cause FP diagnoses.[26,27] In our series, MDM2 FISH analysis on FNA material was not performed, which might have contributed to the FN diagnoses. As with most soft tissue and bone lesions, information about the clinical and radiological picture is mandatory.[28] Although regarded as a tumour with malignant potential, ALT are treated at many sarcoma centres, including our own, as benign lesions without risk for metastatic disease.

Several studies have compared the utility of FNA with CNB analysis in the field of soft tissue and bone pathology. Most studies revealed that CNB is slightly superior to FNA analysis in differentiating between a benign and a malignant lesion, with 80%-93% correct results,[3,7,13,29,30] and our own findings, with a general sensitivity/specificity of CNB diagnoses of 94% and 95%, respectively, have similar results. The same tendency can be found in accuracy analyses, ranging in literature data from 45% to 86%.[13,29] Our own analyses revealed a 90% accuracy of CNB diagnoses among those cases where a specific histological diagnosis was given, accounting for a 66% accuracy of all CNB specimens, excluding cases without surgical follow-up. However, the summary of FP and FN results of both FNA and CNB analyses (Table 4) shows that CNB diagnoses were not always superior to FNA diagnoses. In one case of a chondroblastic osteosarcoma, the FNA material showed atypical cells, suspicious for malignancy whereas the CNB material was interpreted as a benign chondroid tumour. Furthermore, in seven cases, both FNA and CNB analyses resulted in a FP or FN diagnosis. At the puncture service of the Department of Pathology/ University Hospital Lund, FNA and CNB samples are taken simultaneously in the same puncture session. The FNA results are discussed the same day with the clinical staff (orthopaedic surgeons, oncologists and radiologists) and are subsequently completed with CB and CNB results. The patient management depends on both FNA and CNB results. Treating both sampling techniques as one diagnostical procedure and excluding only those cases with insufficient material for both FNA and CNB specimen results in 494 analysable cases. Analyses for this combined approach revealed sensitivity and specificity of 95% and 95%, respectively. This shows that FNA and CNB might complement each other and that a combined FNA and CNB sampling might be an effective way to evaluate the malignant potential of a soft tissue or bone lesion, as suggested previously.[30,31]

In the current study with cases from 2004 to 2014 ancillary techniques such as immunocytology/immunohistochemistry and genetic

TABLE 6 Proposal reporting system soft tissue cytopathology and risk of malignancy (grey shade)

	I. Non-diagnostic	II. Non-neoplastic	III. AUS	IVa. Neoplasm benign	IVb. Neoplasm UMP	V. Suspicious for malignancy	VI. Malignant
Of total n (%)	24 (3)	66 (9)	11 (2)	339 (46)	70 (10)	32 (4)	190 (26)
n (% within classification group)							
Final diagnosis benign	14 (58)	66 (100)	6 (54)	329 (97)	51 (73)	9[a] (28)	5[a] (3)
Final diagnosis malignant	10 (**42**)	— (**0**)	5 (**46**)	9[b] (**3**)	19 (**27**)	23 (**72**)	184 (**97**)
Final diagnosis UMP	—	—	—	1 (0,3)	—	—	1 (0,5)

Abbreviations: AUS, atypia of unknown significance; UMP, unknown malignant potential.

[a]False-positive cases, for details see Table 4.

[b]False-negative cases, for details see Table 4.

analyses were only applied on a fraction of FNA/CB and CNB specimens and were thus not in focus when reporting the results. Those have to be interpreted in a more *historical* context as the diagnostic approach, especially regarding genetic analyses has radically changed in recent years. Immunocytology/immunohistochemistry and FISH analysis are nowadays used to a much higher extent as surrogate diagnostic markers on both FNA/CB and CNB material. In the current study, many specimens were subjected to chromosome banding analysis. Due to the high failure rate on FNA and CNB specimens (approximately 50% and 20%, respectively[32]) it is no longer used for samples with low volume. Chromosome banding in our department has largely been replaced by genomic arrays for CNB specimens. Massive parallel sequencing-based methods will affect and improve the results even further.

The limited role of FNA cytology in the diagnosis of primary soft tissue tumours depends mainly on the rarity of the neoplasms and the lack of experience in the cytological diagnosis of soft tissue lesions. Additional limitation depends on current classification and reporting confusion of soft tissue FNA. Nomenclature, classification and reporting of soft tissue neoplasms used in daily clinical practice is based on the *Soft Tissue and Bone Tumours, WHO Classification of Tumours*.[33] Apart from this classification, a diversity of diagnostic categories based on presumed histogenesis, predominant cell type, cytoarchitectural features or descriptive diagnosis has been used in the classification and reporting of the soft tissue FNA analyses. A standardised cytology nomenclature and reporting system such as for thyroid or salivary gland cytopathology does not yet exist for soft tissue tumours. However, such a reporting system might improve and simplify clinical management of patients with soft tissue lesions. In addition, a standardised classification and reporting system could improve communication among pathologists and promote further research in soft tissue cytology. We tested the case collection of the current study on a reporting system presented at the ECC 2019 in Malmö, with six categories, covering both non-neoplastic and neoplastic conditions. The results show that sampling error is an important issue in soft tissue FNA cytology with a risk of malignancy of 42% in category I (non-diagnostic) and should encourage resampling. In our series there was no or a very low risk of malignancy in the II (0%) and IVa (3%) categories, and high risks for malignancy in both the V (72%) and VI (97%) categories. These clear results can be linked to treatment recommendations and might be useful for patient management. In our opinion intermediate categories such as III and IVb are mandatory in soft tissue cytopathology, mirroring the heterogeneity within this large diagnostic field. In our series, the risk for malignancy was 46% (III) and 27% (IVb), respectively. The value of those categories in a reporting system has been shown for example through the Milan System for Reporting Salivary Gland Cytopathology.[10] Intermediate categories help on the one hand to keep the benign and malignant categories as homogeneous and clean as possible. On the other hand, there is the risk of overusing those categories, especially when lacking experience in the diagnostic field.

All results (sensitivity/specificity analyses, accuracy analyses, proposal reporting system) in the present study were not only based on the cyto-/histomorphological picture but also on the clinical setting and, if available radiological findings. The authors are aware that the results of the current study are based on material coming from a specialised sarcoma centre and provides a slightly biased picture of soft tissue cytopathology. Continuing work is necessary to develop and test a new robust and universal reporting system.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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