THE ROLE OF CYTOLOGY IN THE DIAGNOSIS OF MUSCULOSKELETAL NEOPLASMS: SYSTEMATIC REVIEW

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ABSTRACT

The authors systematically reviewed the literature of the last decade on the role of cytology in the evaluation of musculoskeletal neoplasms, and its diagnostic accuracy. A search was carried out on the databases PubMed, MEDLINE, LILACS and SciELO, selecting articles in which cytology was used in the diagnosis of musculoskeletal neoplasms. Limits were used for English, Spanish and Portuguese, and only articles published since 2000 were selected. 757 articles were retrieved, 24 of which were selected based on criteria of inclusion and exclusion. It was concluded that although promising in the assessment of musculoskeletal neoplasms, cytology obtained by fine needle aspiration is less accurate and reliable than histological evaluation of such lesions.

Keywords: Bone neoplasms. Sarcoma. Muscle, skeletal. Biopsy, needle.

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INTRODUCTION

Primary musculoskeletal neoplasms are relatively rare lesions, and biopsy is an essential step in their diagnosis, closing the classical triad of Jaffe - clinic-radiology-histology –that is so important in these lesions.

In the past, the open biopsy was the gold standard, obtaining an enormous quantity of material to study, yet this method was very invasive, with a high probability of tumor dissemination and other local complications,[1] besides requiring hospitalization and regional or general anesthesia, increasing the costs of the procedure.[1] This did not represent a major problem, due to the very poor prognosis and high rate of amputations of these lesions at that time.

With the change of prognosis and the possibility of conservative surgery, percutaneous biopsy using large gauge needles, trephines – the core biopsies – that are much less morbid and invasive, obtaining sufficient material for diagnosis between 80 and 98% of the cases, began to constitute the gold standard.[2]

The histopathological examination, used to evaluate this material, demands a variable period of some days for fixation and tissue preparation, especially long in bone tumors that require decalcification.

As the results of cytopathology can be obtained from a few minutes to a few hours and the method uses a much smaller quantity of tissue, its use would be very helpful in the diagnosis of musculoskeletal neoplasms, minimizing the invasiveness of the procedure[2-6] and anticipating the biopsy result as much as possible.[5]

The results obtained by fine needle aspiration and cytological study of these lesions, however, are not considered adequate, since they do not yet achieve the same level of success rates as histology in most papers found in the literature.[1-3,6-13]

The aim of this study is to systematically review the literature of the past decade on the role of cytology in the evaluation of musculoskeletal neoplasms and its diagnostic accuracy.

METHOD

A search was carried out in the databases BIREME, PUBMED and LILACS, cross-referencing the descriptors bone neoplasms and fine needle aspiration, and sarcoma and fine needle aspiration in Portuguese, English and Spanish.

Case reports, revisions, animal experiments, *in vitro* trials, studies involving neoplasms from a system other than the musculoskeletal system, and trials limited to describing the cytopathological characteristics of lesions, besides those in languages other than Portuguese, English and Spanish were excluded, selecting articles from the past decade, i.e., as of 2000.

The bibliographic search was carried out in September and October 2010.

All the authors declare that there is no potential conflict of interest referring to this article.

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757 articles were obtained, and 607 were eliminated after the reading of title. Of the 150 abstracts read, 96 were eliminated, with 24 articles remaining after the reading of the complete text and exclusion of repetitions. (Figure 1)

As the evaluated variables as well as the type of lesion assessed and the mode of expression of the data were extremely different among the papers, it was not possible to perform a meta-analysis.

Some authors expressed the data in fractions, which were transformed into percentages to facilitate data comparison.

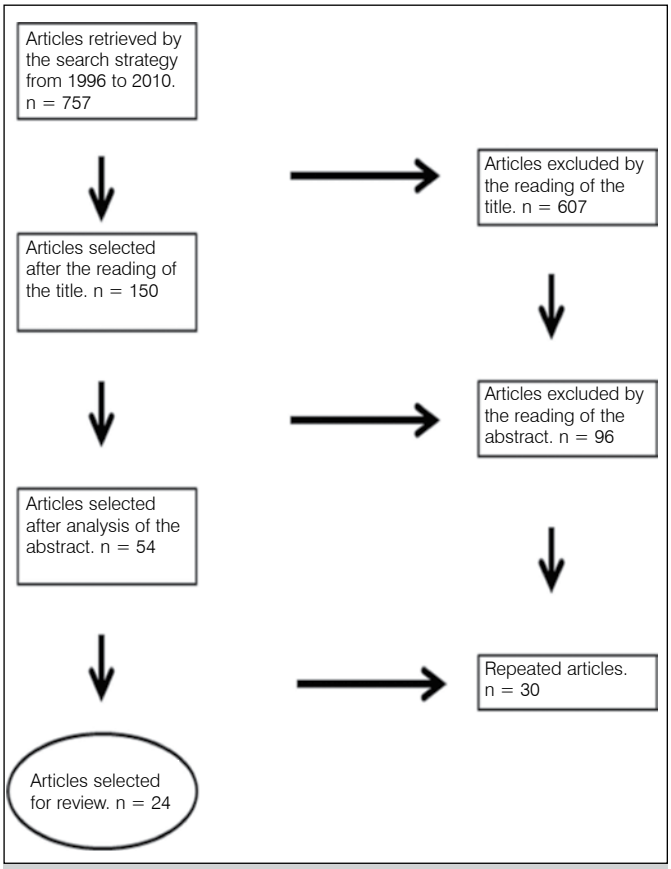

Figure 1. *Flowchart used to select the articles.*

RESULTS

For a better presentation of results, we considered the analysis of the following variables: sample, sensitivity, specificity, correctness of the specific diagnosis, positive predictive value, negative predictive value, accuracy, false benign, false positive and use of supplementary techniques, which were compiled in a contingency table. (Table 1)

DISCUSSION

After the analysis of the studies we were able to verify that few authors dedicate their time to studying cytology in the diagnosis of musculoskeletal lesions, as shown by the distribution of papers in which five practices are responsible for more than 70% of the papers (17 of the 24).

Open biopsy or percutaneous needle trephination are considered the current "gold standard" techniques for obtainment of adequate material for the diagnosis of musculoskeletal lesions by the authors mentioned here, due to the quantity of sample obtained, and their morbidity and invasiveness are always subject to comments.[7,8,14,15]

Cytology, obtained by fine needle aspiration, presents theoretical advantages over the conventional technique as it is less invasive,[5,6,10,15] causes less contamination of the surrounding tissues with neoplasm,[7] is less financially onerous[1-3,5,6,8,10,15] and presents a faster result,[5,7,10] although its usefulness in musculoskeletal neoplasms is contradictory.[3,7,8,16]

The various reasons mentioned for the above phenomenon are: inability to evaluate tissue architecture;[8,16] difficulty obtaining an appropriate sample,[2-4,6,9,17,18] difficulty recognizing the extracellular matrix, especially osteoid;[9,19] considerable variability in histological patterns[6] with similar aspects both among different malignant lesions and among benign, malignant and non-neoplastic lesions,[2,4,7,9, 16,19,20] difficulty in the histologic subtyping and grading of lesions.[7,8,12,13,19,21] It could be noted that few authors base the definitive treatment exclusively on cytopathological results[5,7-10], which demonstrates that despite the degree of precision referred to by the authors, there is limited confidence in the method.

To optimize the data obtained by the sparse sample, the authors stress the need for intense integration of the interdisciplinary team,[7-10,12,15] since part of the subtype diagnoses were based on the imaging tests and clinic examination. Moreover, it appears highly recommendable to use supplementary methods such as electronic microscopy, histochemistry, immunohistochemistry and cytogenetics, which were mentioned directly by half of the authors.[1,6-12,15,17,21]

Sensitivity, that is, the ability to distinguish between benign and malignant lesions, among the authors who expressed these data from their populations, ranged from 65[3] to 100%,[10,11,22] which is close to those of the more invasive methods.

The ability, however, to determine an accurate diagnosis, expressed by the authors as specificity,[2,3,6,8] accurate diagnosis[1,5,9,12-15,17,21] or accuracy,[2,7] varied widely from 14[23] to 100%.[6,16,21] The variability in the type of measurement adopted by the authors hinders the comparison of data, yet it is possible to perceive the major variation among values, showing that cytology presents different precisions in the various clinical situations.

Several factors appear to influence the precision of the exam, while the diagnosis is noticeably more difficult in neoplasms of the soft tissues, fusocellular lesions (a very frequent histological pattern among both benign and malignant lesions),[4,8,17,19,21,23] as well as in primary lesions (when compared to recurrences and metastases).[1,7,8,16]

The above fact leaves it clear that knowledge of the primary lesion or the assumption of malignancy decisively influences the cytopathologist, possibly because the cytologic sample does not provide as much information on the studied tissue as histology, justifying the need for such considerable integration of clinical, radiological and cytopathological information to reach a trustworthy diagnosis.

The great difficulty of cytology in determining the accurate diagnosis of the lesion or its histological subtype is an important item of data, since while for some lesions simple determination of malignancy is sufficient to determine the treatment, in most

Table 1. *Selected studies that evaluated the use of the fine needle aspiration in musculoskeletal neoplasms.*

Author/year	Type of Lesion	Histological Subtype	Results (in Percentage)
Dalén/2006	ST	Desmoid	Cytology n = 69; s = 88.4; e = Ø; d = 50.7; f = 5.8; ppv = Ø; a = Ø; fb = Ø; fm = 5; st = Ø. Histology n = 26; s= 100; e = Ø; e = Ø; d = 92.3; f = Ø; ppv = Ø; a = Ø; fb = Ø; fm = 0; st = Ø.
Dey/2004	ST		Cytology n =82; s =91.5; e = 92.5; d = Ø; f = Ø; ppv = 95.5; a = Ø; fb = 8.5; fm = 4.2; st = Ø.
Dodd/2002	BONE	Osteosarcoma	Cytology n = 40; s = 65; e = Ø; d = Ø; f = 15; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st = Ø.
Domanski/2006	ST	Leiomyosarcoma	Cytology n =89; s =87.6; e = Ø; d =34.8; f =8.9; ppv = Ø; a = Ø; fb =3.37; fm = Ø; st =yes. Diagnosis of Sarcoma = 83.1
Domanski/2006	ST	Neurilemmoma	Cytology n =116; s = 69; e = Ø; d =57.7; f =26; ppv = Ø; a = Ø; fb = Ø; fm =5; st = yes.
Domanski/2005	BONE	Osteosarcoma	Cytology n =59; s =83; e = Ø; d =74.6; f =17; ppv = Ø; a =; Ø fb =0; fm =0; st = yes.
Fleshman/2007	ST		Cytology n =107; s =94; e = Ø; d = Ø; f =9.3; ppv =97; a =91; fb = Ø; fm = 3,2; st = yes.
González Díaz/2004	BONE		Cytology n =21; s = 71.4; e = Ø; d = Ø; f = 28.5; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st = Ø.
Huening/2008	BONE	Fibrous Dysplasia	Cytology n = 6; s = Ø; e = Ø; d = 33; f = 67; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st = Ø.
Jakowski/2010	BOTH		Cytology n = 141; s = 100; e = 96; d = 71.6; f = Ø; ppv = 88; a = Ø; fb = Ø; fm = Ø; st = Ø.
Jorda/2000	BONE		Cytology n = 314; s = 92; e = 99; d = Ø; f = 31; ppv = 99; a = 95; fb = 1.17; fm = 2.9; st = Ø.
Khalbuss/2010	BOTH		Cytology n = 1114; s = 96; e = 98; d = Ø; f = 7.5; ppv = 99; a = Ø; fb =1.35; fm = 0.27; st = yes. Bone n = 273; s = 93; e = 100; d = Ø; f = Ø; ppv = 100; a = Ø; fb = Ø; fm = Ø; st = yes. ST n = 841; s =97; e =97; d = Ø; f = Ø; ppv =99; a = Ø; fb = Ø; fm = Ø; st =yes.
Kilpatrick/2000	ST	Myxoid Sarcoma	Cytology n =16; s = 93.7; e = Ø; d = 81; f = Ø; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st = Ø.
Kilpatrick/2001	BOTH		Cytology n =145; s = Ø; e = Ø; d = Ø; f =4.8; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st = yes. Bone n =49; s = 93; e = Ø; d =82; f = Ø; ppv = Ø; a = Ø; fb =2; fm = Ø; st =yes. ST n =86; s =86; e = Ø; d =54; f = Ø; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st =yes. Pediatric n = Ø s = Ø; e = Ø; d =92 Ø; f = Ø; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st = yes Adult n = Ø; s = Ø; e = Ø; d =52; f = Ø; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st = yes.
Klijanienko/2003	ST	Malignant Fibrous Histiocytoma	Cytology n =95; s =95.8; e = Ø; d =24.2; f =4.2; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st = yes. Primary n =44; s =95.4; e = Ø; d =13.6; f =4.6; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st =yes.
Klijanienko/2003	ST	Angiosarcoma	Cytology n =29; s =89.7; e = Ø; d =58.6; f =10.3; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st =no. Primary n = 16; s =87.5; e = Ø; d =37.5; f =12.5; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st =no.
Klijanienko/2004	ST	Benign Fibrous Histiocytoma	Cytologyn = 36; s =91.7; e = Ø; d =61.1; f = Ø; ppv = Ø; a = Ø; fb =8.3; fm = Ø; st =no.

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Author/year	Type of Lesion	Histological Subtype	Results (in Percentage)
Klijanienko/2007	ST	Rhabdomyosarcoma	Cytology n =180; s = 99.5; e = Ø; d = Ø; f =0.005; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st =yes. Primary n = 58; s =98.3; e = Ø; d =74.1; f = Ø; ppv = Ø; a = Ø; fb =1.7; fm = Ø; st = yes.
Klijanienko/2007	BONE	Osteosarcoma	Cytology n =126; s =95.3; e = Ø; d = Ø; f =3.1; ppv = Ø; a = Ø; fb =1.6; fm = Ø; st = Ø. Primary n =55; s =91; e = Ø; d =43.6; f =5.4; ppv = Ø; a = Ø; fb =3.6; fm = Ø; st = Ø.
Klijanienko/2003	BOTH	Leiomyosarcoma	CYTOLOGY n =96; s =100; e = Ø; d =24; f =2.1; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st =yes.
Ng/2010	ST		Cytology n =432; s = Ø; e = Ø; d = Ø; f =8.1; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st =yes. Malignant n =129; s =88.9; e =84.4; d = Ø; f = Ø; ppv =95.1; a = Ø; fb =3.8; fm = Ø; st =yes. Malignant n = 268; s =89.2; e =89.8; d = Ø; f = Ø; ppv =96.1; a = Ø; fb = Ø; fm =1.4; st =yes.
Ward/2000	BONE		Cytology n =66; s = Ø; e = Ø; d =73; f =18; ppv = Ø; a = Ø; fb = 1.5; fm = Ø; st = Ø.
Wedin/2000	BONE	Metastasis	Cytology n =110; s = Ø; e = Ø; d =93; f = Ø; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st =yes. Diagnosis of the primary site = 66.4.
Yang/2004	BOTH		N =50; s = Ø; e = Ø; d = Ø; f = Ø; ppv = Ø; a = Ø; fb = Ø; fm = Ø; st =yes. Cytology = n = 50; s =88; e = Ø; d =68; f = 8; ppv = Ø; a = Ø; fb =2; fm = Ø; st =yes. Histology n =50; s =94; e = Ø; d =86; f =2; ppv = Ø; a = Ø; fb =4; fm = Ø; st yes.

n = samples
s= sensitivity.
e = specificity.
d = accurate diagnosis.
f = frequency of non-obtainment of diagnosis (unsatisfactory, inconclusive sample).
ppv = positive predictive value.
a = accuracy.
fb = false benign.
fm = false malignant.
st = supplementary techniques.
ST = soft tissues.
Ø = not mentioned by the author.

benign lesions, as well as in malignant bone tumors and in some soft tissue sarcomas, the determination of the specific type of lesion defines the initial therapy to be introduced.[7]

As regards the therapeutic decision, it is also essential to emphasize that the number of false positive results ranged from 0.9 to 5%[14] while that of false negatives ranged from 1.17[2] to 8.5%[16] among the authors who expressed these measurements. In other words, benign tumors were diagnosed as malignant and vice versa with catastrophic clinical repercussion, if the treatment is carried out on the basis of this diagnosis.[7]

Only Dalén[14], Yang and Damron[15] made a direct comparison of the cytological results with the histology obtained by core biopsy, in the same sample, clearly evidencing the superiority of the histological analysis in their studies.

In Yang's casuistry, however, the number of false negative cases of histology was double that of cytology. The cases were low-grade lipomatous lesions, which are known to be hard to diagnose by small samples both by core biopsy and by aspiration, since the tissue and cytological alterations suggestive of malignancy presented by these lesions[15] are mild and focal, with diagnosis based on clinical and radiological characteristics.

There was no statistical treatment of data in any of the selected papers, compromising the validity of the conclusions obtained by the authors.

CONCLUSION

Fine needle biopsies are promising in the evaluation of musculoskeletal lesions.

Their use as a unique diagnostic method, however, should be undertaken very carefully, and should be performed in an interdisciplinary context, accompanied by supplementary methods (electronic microscopy, immunohistochemistry and cytogenetics), preferentially for recurrent or metastatic lesions and avoiding certain lesions such as bone of very consistent soft tissues tumors or lesions of fusocellular soft tissues.

Percutaneous biopsy with trephine or core biopsy, despite its greater invasiveness, cost and time for processing when compared to fine needle aspiration, remains the "gold standard" for evaluation of musculoskeletal lesions due to its accuracy and low morbidity.

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