ORIGINAL RESEARCH PAPER

Volume-9 | Issue-2 | February-2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

DIFFERENTIATING MALIGNANT AND BENIGN SOFT TISSUE MASSES ON ULTRASOUND ; GRAYSCALE, DOPPLER AND SPECTRAL WAVEFORM ANALYSIS.

Radiodiagnosis

Dr. Ankit Kumar Shah 3rd year Post-graduate resident, Department of Radiodiagnosis Netaji Subhash Chandra Bose medical college Jabalpur M.P

Dr. Kiran Kumar M* senior resident, Department of Radiodiagnosis Netaji Subhash Chandra Bose medical college Jabalpur M.P *Corresponding Author

Dr. Rekha Agrawal Associate Professor, Department of Radiodiagnosis Netaji Subhash Chandra Bose medical college Jabalpur M.P

Dr. Avadhesh Pratap Singh Professor and Head, Department of Radiodiagnosis Netaji Subhash Chandra Bose medical college Jabalpur M.P

ABSTRACT

Purpose: Of this study is to evaluate the role of greyscale ultrasound and duplex sonography in differentiating benign from malignant musculoskeletal soft tissue masses, in order to assess whether these methods are able to increase the diagnostic accuracy of grayscale ultrasonography.

Materials and methods: all 50 Patients with palpable soft tissue masses of all age groups and both genders were included, excluding Inflammatory masses (like abscesses, cellulitis, and pyomyositis) and trauma. All patients were examined by means of available equipment Mindray DC-30 series ultrasound machine and confirmed by FNAC/histopathology of the masses. Depending on the size and depth of the lesion, curved array or linear probes were used 5-1 MHz and 15-6 MHz, respectively

Results: grayscale ultrasonography showed 75% sensitivity, 63% specificity, 57% positive predictive value, 79% negative predictive value and 68% accuracy in differentiating benign from malignant lesions while combined evaluation ultrasound showed increase; 80% sensitivity, 93% specificity, 88% positive predictive value, 87% negative predictive value and 88% accuracy in differentiating malignant from benign lesions. Low Resistive indices (= or less than 0.5) of the internal vessels within the tumors also showed significant correlation with the malignant nature of the lesion

Conclusion: duplex ultrasound assessment of MSK soft tissue masses might represent an important supplement to greyscale sonography and should always be performed when evaluating the same by ultrasonography.

KEYWORDS

INTRODUCTION

Musculoskeletal soft tissue can be defined as periskeletal non epithelial connective tissue of the body exclusive of reticuloendothelial system representing voluntary muscles, fat and fibrous tissue along with nerves and vessels serving these tissues. Several imaging modalities have been applied to assess these tumors, including plain radiography, nuclear medicine, computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), angiography and positron emission tomography. Most general practitioners, however, find it difficult to distinguish benign from malignant lesions.[1] Among the various imaging modalities, US is most often available clinically. It also has the advantages of being simple, easy and inexpensive, and it can offer results in real-time it helps in detection, delineation and characterisation of musculoskeletal soft tissue lesions. In addition, sonography can easily differentiate solid from cystic lesions, which frequently are benign or posttraumatic. [2-5]

Historically, diagnostic ultrasound imaging has been utilised in medicine since the early 1950's. In the following decades, diagnostic ultrasound imaging became well-established in clinical obstetrics, gynaecology and cardiology. In 1972, the first clinically significant application of diagnostic ultrasound imaging was used in musculoskeletal medicine; where it was used to differentiate Baker's cysts from thrombophlebitis.[6-7]

Recent advances in ultrasound technology have enabled the echotexture of soft tissue tumors to be presented in greater detail. Several previous studies confirmed that intratumoral blood flow was a useful factor for differentiating benign and malignant tumors.[8-9]

Comparative angiographic and pathologic studies have demonstrated that newly formed tumor vessels show distinct features (abnormal branching pattern, irregular size, wide sinusoids, arteriovenous shunts); such features and the resulting blood flow abnormalities can readily be detected by means of color and pulsed Doppler sonography.[10-13]

The purpose of this study was to evaluate the role of color and pulsed Doppler examination in the differential diagnosis of benign from malignant musculoskeletal soft tissue masses, in order to assess whether these methods are able to increase the diagnostic accuracy of grayscale conventional sonography.[12-13]

MATERIALS AND METHODS

This prospective study was conducted in Department of Radiodiagnosis in collaboration with Department of Surgery and Department of Pathology, N.S.C.B. Medical College, Jabalpur. Patients with palpable soft tissue masses of all age groups and both gender were included. Cases with Inflammatory masses (like abscesses, cellulitis, and pyomyositis), post-trauma fluid collections, deep vein thrombosis, thyroid, breast masses and cystic lesions were excluded from the study

All patients were examined by means of available equipment of the department MINDRAY DC-30 series. Depending on size and depth of the lesion curved array or linear probes were used, in cases of irregular skin surface of digits, water bath technique was used.

Color Doppler parameters were optimized for low blood flow velocities. Power Doppler interrogation, when available, also was used for showing more clearly the number and course of afferent and intralesional vessels. For spectral analysis, low values of PRF and low or no wall filters were used; when necessary, the PRF was adjusted for medium to high blood flow velocities. Sample volume was adjusted to the vessel size. Waveforms were recorded at different sites within each mass; for each lesion, a minimum of three measurements was performed. Whenever possible, absolute velocities were calculated after correcting for the angle of incidence. When different peak systolic values were found within the same lesion, the highest values were considered for evaluation.[12,14]

Sonographic features evaluated were growth pattern, margins, echogenicity, and internal texture. Growth pattern was defined as

expansive (rounded or elliptical lesion compressing adjacent structures) or infiltrating (poorly detectable lesion distorting normal structures). Margins were defined as regular (smooth), irregular (shaggy), or blurred (ill defined). Echogenicity was defined as hypoechoic or hyperechoic relative to adjacent muscle tissue. Internal texture was defined as homogeneous or heterogenous (on the basis of necrotic and cystic changes). Malignancy was suspected on the basis of the following criteria: infiltrating tumor growth, irregular or blurred/ill margins, hypoechoic pattern, heterogenous texture. Fulfilment of at least two of these criteria was considered necessary for diagnosing malignancy.[12,13,15] Size as a criteria was also introduced in this study in which 5cm was arbitrarily assumed as a criterion for differentiating malignant from the benign lesion (more than 5cm in any of the axis and taller than wider lesions were considered malignant).[16-17]

On Color Doppler examination, the extent and configuration of tumor vascularity were assessed on the basis of the following features: presence or absence of flow signals, number of afferent vessels (fewer than three versus three or more afferent vessels), vessel arrangement within the lesion (regularly distributed or randomly dispersed, with areas of increased vessel density), vessel course (linear, tortuous, spot flow signals), and presence or absence of abrupt variations in calibre (greater than 50%).[15,18] Malignancy was suspected on the basis of the following criteria: increased vascularisation (three or more afferent vessels), irregular arrangement of tumor vessels, tortuous vessel course or spot flow signals, or presence of abrupt variations in calibre. Malignancy was diagnosed when at least two of these signs were present.[12,13]

On pulsed Doppler evaluation, the parameters measured were: peak systolic velocity and resistive index. The RI was defined by the following equation: (peak systolic velocity - end-diastolic velocity)/peak systolic velocity. A threshold value of 0.50 m/s for systolic velocity and of 0.50 for RI, was arbitrarily assumed as a criterion for discriminating benign from malignant lesions (PSV less than 0.50 m/s = benign; 0.50 m/s or greater = malignant; similarly RI less than 0.50 = malignant ; greater than 0.50 = benign).. Malignancy was diagnosed when at least one of positive finding was present.[19-20]

Definitive diagnosis was provided by histological study by FNAC/Biopsy for all the patients based on the World Health Organization classification system.[21] All the patients provided written permission to use their samples.

STATISTICAL ANALYSIS

Quantitative data are presented as the means ± standard deviation. The Mann-Whitney U, Fisher's exact and $\chi 2$ tests were used for unpaired comparisons between the quantitative parameters. A value of $p<0.05$ was considered to indicate a statistically significant difference.

RESULTS

The lesions ranged in size from 0.5cm to 16cms mean (5.2±2.1cms) and the lower limb being the most frequent site (26/50 cases)

Histological examination showed presence of 20 malignant and 30 benign cases. Among the benign the histological diagnosis were lipoma (n=11), benign spindle cell tumor (n=4), carotid body mass (n=1), arteriovenous malformation (n=5), giant cell tumor (n=2), myoma (n=1), neurofibroma (n=2), schwannoma (n=1), fibromatosis colli (n=1), glomus tumor (n=2)

Amongs the malignant lesions the histological diagnosis were ewings sarcoma (n=4), secondary metastatic lymphnode (n=4), liposarcoma (n=3), lymphoma (n=2), malignant spindle cell (n=1), malignant fibrous histiocytoma (n=2), malignant melanoma (n=1), malignant squamous cell carcinoma (n=2), rhabdomyosarcoma (n=1). Table – 1

Table-1 Sonographic and color Doppler findings (summarized in Tables 2 and 3) were reviewed retrospectively.

Malignant	n
Ewings Sarcoma	4
Secondary Metastatic Lymphnode	4
Liposarcoma	3
Lymphoma	2
Malignant Spindle Cell	1
Malignant Fibrous Histiocytoma	2
Malignant Melanoma	1
Malignant Squamous Cell Carcinoma	2
Rhabdomyosarcoma	1
Benign	n
Lipoma	11
Benign Spindle Cell Tumor	4
Carotid Body Mass	1
Arteriovenous Malformation	5
Giant Cell Tumor	2
Myoma	1
Neurofibroma	2
Schwannoma	1
Fibromatosis Colli	1
Glomus Tumor	2

On the basis of sonographic criteria, 34 of 50 cases were correctly evaluated as malignant (15 of 20 cases) or benign (19 of 30 cases). 11 false-positive results were noted and Five false-negative, showing 75%sensitivity, 63% specificity, 57% PPV, and 79% PPV of the procedure, with an overall 68% accuracy. On combining size as the parameter (using cut-off of 5cm and more for malignant nature) we were able to correct the diagnosis in four false positive and in one false negative case thus achieving correct diagnosis in five more cases and increase in accuracy (74%). Two of the cases which had depth more than their length were diagnosed as malignant (fig 1,2)

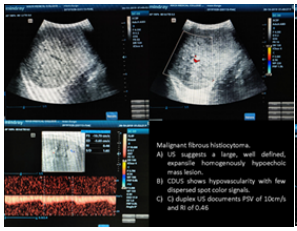

FIGURE: 1

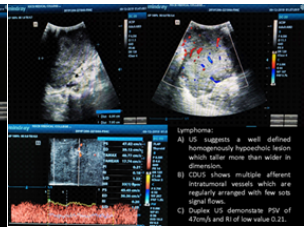

FIGURE: 2

Features that showed significant or highly significant correlation with malignant nature of the lesion include irregular margins ($p<0.05$), infiltrating growth pattern ($p<0.05$), heterogenous internal texture($p<0.05$) and size more than 5cms ($p<0.001$). Echogenicity of the lesion (hypoechoic or hyperechoic) showed nonsignificant (p-value >0.05) correlation with benign/ malignant nature of the lesion. (fig 3,4,7,8)

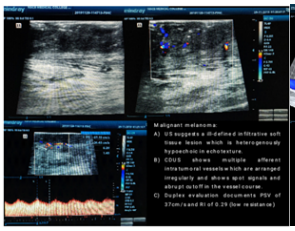

FIGURE : 3

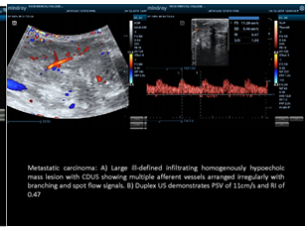

FIGURE: 4

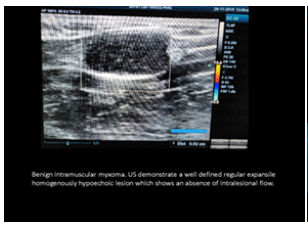

FIGURE : 5

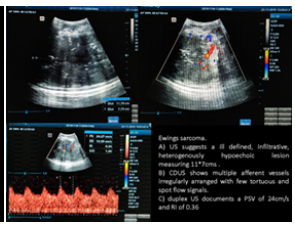

FIGURE: 6

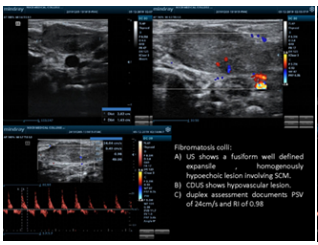

FIGURE : 7

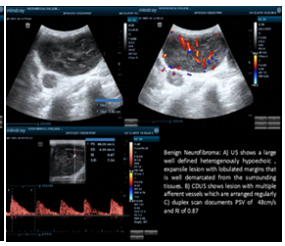

FIGURE: 8

On color Doppler sonography, flow signals were found in 22 of 30 (73.33%) benign lesions and in 20 of 20 (100%) malignant lesions. Absence of flow was found for benign lesions only 8 of 30

(26.66%).Benign lesions (lipoma-5, benign spindle cell tumor-1, myoma-1, neurofibroma-1) showed no flow on either color or power Doppler interrogation. (fig 6)12-14

Based on color Doppler criteria, 41 of 50 cases were correctly evaluated as benign (27 of 30 cases) or malignant (14 of 20 cases). three false-positive and six false-negative results were obtained, for 70%sensitivity, 90% specificity, 82% PPV, and 81% NPV, with an overall 82% accuracy of the procedure.

All Color Doppler analysis data showed highly significant (p-value < 0.001) correlation with their respective kind of nature of the lesion (benign/malignant). A regularly distributed arrangement of vessels with linear course and lesser than 50% abrupt variation in calibre of vessels showed highly significant correlation with benign nature of the lesion . In contrast, randomly dispersed arrangement of vessels with tortuosity and greater than 50% abrupt variations in calibre of vessels showed highly significant(p-value <0.001) correlation with malignant nature of the lesion.

Concerning quantitative spectral analysis, PSV values of flow signals did not show a significant difference between benign and malignant lesions: however five of 20 malignant lesions and two of 22 benign lesions showed velocity of more than 0.50m/s. In contrast, RI value showed a good correlation between lower resistance waveform pattern (less than 0.5) and malignancy: 11 of 20 (55%) malignant lesions showed Resistive index less than 0.5 and 21 of 22 (95%) benign lesions showed RI of more than 0.5, with 9 false negative and 1 false positive results with highly significant correlation (p-value <0.001). (Table-4). The resistive indices of the benign masses ranged from 0.45 to 0.98 (mean ± SD, 0.72 ± 0.13) whereas the malignant masses had resistive indices ranging from 0.20 to 0.90 (mean ± SD, 0.52 ± 0.18) (fig 5,9,10)

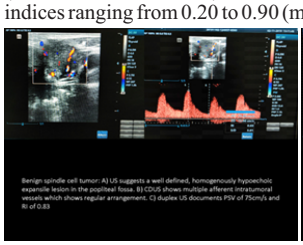

FIGURE :9

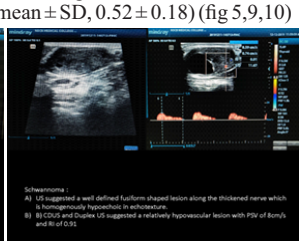

FIGURE :10

Finally, by combining sonographic findings with color and duplex data, a correct diagnosis of benign versus malignant was obtained in 44 of 50 patients (88%), with 2 false-positive and 4 false-negtive results. The overall accuracy of such combined assessment based on morphology and color and spectral Doppler findings was 88%, with 80% sensitivity and 93% specificity (88% PPV, 87% NPV) (Table 5).

Table-2: Comaparison with grayscale of malignant and benign tumor

Grayscale pattern	Malignant n=20	Benign n=30	P value
Growth pattern Expansive Infiltrative	 15 5	 29 1	<0.05 Significant
Margin Regular Shaggy Ill defined	 13 2 5	 27 0 3	<0.05 Significant
Echogenicity Hypoechoic Hyperechoic	 19 1	 28 2	>0.05 Not significant
Internal texture Homogenous Heterogenous	 6 14	 20 10	<0.05 Significant
Size >5cm <5cm	 12 8	 4 26	<0.001 Highly significant

Table-3:Color Doppler Findings for Vascularized Lesions

Colour signal patterns	Malignant n=20	Benign n=30	P value
Avascular Less than 3 afferent vessels More than 3 afferent vessels	0 5 10	8 12 10	>0.05 Not significant
Arrangement Regular Irregular	 10 10	 21 1	<0.001 Highly significant
Abrupt calibre variation >50% Present Absent	 10 10	 2 20	<0.001 Highly significant
Spot/tortuous flow Yes No	 12 8	 3 19	<0.001 Highly significant

Table-4: Spectral waveform findings for the vascularised lesions

Waveform patterns	Malignant n=20	Benign n=22	P value
PSV >0.5m/s <0.5m/s	 5 15	 2 20	>0.05 Not significant
RI <0.5 >0.5	 11 9	 1 21	<0.001 Highly significant

Table-5: Sensitivity, Specificity, NPV, PPV, and Accuracy

	Sensitivity	Specificity	PPV	NPV	Accuracy
Grayscale ultrasound	75	63	57	79	68
Color Doppler ultrasound	70	76	66	79	74
Spectral/Duplex analysis	65	81	76	72	73
Combined evaluation	80	93	88	87	88

DISCUSSION

Soft tissue tumors are commonly found in the everyday practice of general surgeons, including orthopedic surgeons. The incidence of malignant soft tissue tumors is low, accounting for <1% of all neoplasms. In contrast, benign soft tissue tumors occur rather frequently.4 Several imaging modalities have been used to assess soft tissue tumors, with CT and MRI playing a key role. Several authors.[22-24] Noted that only MRI and CT can assess the possible components of the tumors and can show their anatomic location and extent. It provides important information for a preoperative diagnosis and for planning surgery.[25]

We focused on US as a powerful candidate for screening patients for soft tissue tumors. US is non-invasive, has a low cost, and is widely available compared with CT and MRI. It is also possible to perform US in an ambulatory practice. To date, however, little evidence-based information has been available concerning the use of US to evaluate soft tissue tumors. Hence, we decided to test the usefulness of US with the latest material available to determine if it can contribute to distinguishing between benign and malignant soft tissue tumors. Role of sonography in the study of musculoskeletal soft tissue masses is, however, impaired by its poor specificity and lack of panoramic representation of compartmental anatomy.

Conversely, since color Doppler imaging can depict tumor vascularity and flow, it provides information that may assist in distinguishing benign from malignant lesions. Pathologic and microangiographic studies have demonstrated that malignant tumors form tortuous, deformed and displaced vascular structures that may be highly unstable and immature. They are characterized by a high proliferation of endothelial cells, hyperpermeability and chaotic blood flow.[26]

Compared with normal tissue, such newly formed vessels have a different internal structure, characterized by lack of smooth muscle in arterial walls, arteriovenous fistulae, and large sinusoids. [11-12]

In this regard, color Doppler imaging and spectral analysis offer unique information that cannot be obtained by other imaging techniques and that might prove useful in diagnosis.[11-14]

To date, as specifically concerns musculoskeletal soft tissue masses, color Doppler studies on this topic are quite scant in the literature.

According to *Ozbek and co-workers*[27] color Doppler sonography is not able to differentiate benign from malignant masses, although spectral analysis seems useful in differentiating acute inflammatory diseases (which show decreased impedance) from neoplasms (which show increased impedance).

According to other authors[12,14], in contrast, careful analysis of the number and spatial arrangement of tumor vessels in subcutaneous lesions allows a significant improvement of diagnostic accuracy to be achieved.

In the present study, malignancy was under appreciated by grayscale imaging. Benign and malignant lesions in our series often shared similar sonographic appearances. In our experience, however, lipomas in unusual locations (e.g., intramuscular lipomas) may have misleading features. Sonographic presentation of other lesions is nonspecific.

As a consequence, among all the features examined (growth pattern, margins, echogenicity, texture) no morphologic criteria—either alone or in combination—were present that could allow a confident diagnosis of benign versus malignant lesion.

Lange et al[28] noted that soft tissue masses with an ill-defined appearance on US may be assumed to be benign. In the present study, most tumors had a well-defined appearance, whereas an ill-defined appearance was considered malignant; quite different from the report of *Lange et al*.[28] Advances in image resolution enabled this distinction.

Chiou et al[29] and *Belli et al*[12] reported that growth pattern, tumor margin, heterogeneous echotexture and size seemed to be significant indicator for differentiating the lesion which is consisitent with our present study. However shape and echogenecity were not significant in any of these mentioned studies. Size (more than 5cms) and taller than wider were found to be significant in our study which is also consistent with the studies done by *T. Morri et al*[16] and *S. Nagano et al*[17]

Color and pulsed wave Doppler data were more helpful. Absence of flow (in 8 of 30 benign lesions; 26.6%) was found for benign lesions only; this feature therefore was strongly significant, with a highNPV (100%). Presence of flow, conversely, was not discriminating, since it was found in 22 of 30(73.3%) benign lesions as well as in 20 of 20 (100%) malignant lesions. Even a higher number of afferent vessels (more than three) was not significant, since it correlated to a great extent with tumor size and not only with its benign or malignant nature. A regular arrangement of vessels with a linear course was suggestive of a benign mass. In contrast, randomly distributed vessels with abrupt variations in size as well as spot flow signals were fairly typical of malignancy; such features might be related to native vessel infiltration or to irregular tumor angiogenesis. [12-15,18]
Belli et al[12] demonstrated that conventional sonography was not reliable for diagnosing malignancy , whereas colour Doppler, power Doppler and spectral analysis were quite useful.

Lagalla et al[13] stated that malignant potential was indicated in the presence of three or more vascular signals and tortuous and irregular internal vessels seen by CDUS . these were consistent with our present study.

With regard to spectral analysis, arterial resistance as well as diastolic and peak systolic velocities were not significantly different in our study. Instead, resistive index was quite useful in the differential diagnosis between benign and malignant lesions; in our series, this was the reliable parameter for discriminating benign and malignant lesions.

A threshold of 0.5 was best suited for distinction of benign from malignant tumours. By assuming this threshold value, we were able to correctly identify 11 of 20 malignant lesions and 21 of 22 benign lesions.

Diagnostic accuracy was further improved by combining sonographic findings with color and pulsed Doppler data. A correct diagnosis of benign versus malignant was obtained in 44 of 50 patients (88%), with 2 false-positive and 4 false-negative results. The overall accuracy of such combined assessment based on morphology and color and spectral Doppler findings was 88%, with 80% sensitivity and 93% specificity (88% PPV, 87% NPV) *Kaushik et al*[19] demonstrated that however evaluation of RIs was found to be unreliable in differentiating benign from the malignant but the data suggested that a lesion with RI of less than 0.5 is likely to be malignant and RI of more than 0.5 cannot distinguish between them.

Bodner et al[20] discovered that the RI ratio was an indicator of malignancy. The present study suggested RI value less than 0.5 was significantly reliable in differentiating benign from the malignant

Our study was consistent with various different previous studies (Table-6)

Table-6:Study comparison with various other studies

Author (Refs.)	Patient Result	(%)
Giovagnorio et al [11]	71 Nodules	CDUS: Sensitivity (90) Specificity(100)
Lagalla et.al [13]	46 Soft-tissue masses	US: Sensitivity (75) Specificity (50) Accuracy (61)
Belli et al [12]	36 Benign tumors 20 Malignant tumors	US: Sensitivity (60) Specificity (55) Accuracy (57) CDUS: Sensitivity (85) Specificity (88) Accuracy (87) COMBINED: Sensitivity(90) Specificity (91) Accuracy (91)
Naoto Oebisu et al [30]	118 Benign tumors 62 Malignant tumors	CDUS: Sensitivity (55) Specificity (77) Accuracy (69)
Present study	30 Benign tumors 20 Malignant tumors	US: Sensitivity (70) Specificity (76) Accuracy (74) CDUS: Sensitivity (70) Specificity (90) Accuracy (82) COMBINED: Sensitivity (80) Specificity (93) Accuracy (88)

CONCLUSION

By our study we concluded that we can use B-mode, color Doppler ultrasonography and spectral wave analysis for assessing musculoskeletal soft tissue masses with good accuracy, sensitivity, specificity, positive predictive value and negative predictive value.

We can reliably differentiate benign from malignant soft tissue masses by using morphological as well as color Doppler features which were consistent with FNAC and biopsy.

Low Resistive indices (= or less than 0.5) of the internal vessels within the tumors also showed significant correlation with the malignant nature of the lesion. Thus spectral wave analysis can reliably differentiate benign from malignant soft tissue masses on the basis of resistive indices.

We acknowledge that Doppler assessment of tumor vascularity has inherent limitations: variations in results and diagnostic errors can be expected owing to the complex vasculature of neoplasms and the potential sources of error involved in Doppler assessment.

First, tumor size and anatomo-pathologic changes of tumor vascularization may affect hemodynamic patterns. Tumor vascularity varies during different phases of tumor growth, since with progressive enlargement, areas of hypoxia and necrosis occur, so that both hyperaemic and avascular areas can be found within the same lesion.[11]

Second, Doppler calculation of systolic velocity can be impaired when angle correction is impossible because the vessel course cannot be identified (as in spot flow signals).[31]

Our conclusions are based on a limited number of patients and should be validated on a larger series. In addition, the study population represented only some of the many different types of soft tissue tumors that can be encountered.

Our data, however, suggest that color and duplex assessment might represent a useful adjunct to grayscale and should be routinely performed when evaluating musculoskeletal soft tissue masses by ultrasonography

REFERENCES

1. Kransdorf MJ and Murphey MD: Radiologic evaluation of softtissue masses: a current perspective. AJR Am J Roentgenol 175: 575-587, 2000
2. Bottinelli O., Campani R. (2001) Ultrasound of the Hand. In: Guglielmi G., van Kuijk C., Genant H.K. (eds) Fundamentals of Hand and Wrist Imaging. Springer, Berlin, Heidelberg
3. Johnstone AJ, Beggs I: Ultrasound imaging of softtissue masses in the extremities. J Bone Joint Surg [BR] 76:688, 1994.
4. Simon MA, Finn HA: Diagnostic strategy for bone and soft-tissue tumors. J Bone Joint Surg [Am] 75:622, 1993 J Ultrasound Med 19:823–830, 2000 BELLI ET AL 829.
5. Dock W, Grabenwöger F, Metz V, et al: Tumor vascularization: Assessment with Duplex sonography. Radiology 181:241, 1991.
6. McDonald DG, Leopold GR. Ultrasound B-scanning in the differentiation of Baker's cyst and thrombophlebitis. Br J Radiol197;45:729–32.
7. Cooperberg PL, Tsang I, Truelove L, Knickerbocker WJ. Gray scale ultrasound in the evaluation of rheumatoid arthritis of the knee. Radiology 1978; 126:759–63.
8. Widmann G, Riedl A, Schoepf D, Glodny B, Peer S and Gruber H: State-of-the-art HR-US imaging findings of the most frequent musculoskeletal soft-tissue tumors. Skeletal Radiol 38: 637-649, 2009.
9. Gielen J., Ceulemans R., van Holsbeeck M. (2006) Ultrasound of Soft Tissue Tumors. In: De Schepper A.M., Vanhoenacker F., Gielen J., Parizel P.M. (eds) Imaging of Soft Tissue Tumors. Springer, Berlin, Heidelberg.
10. Fleischer AC: Sonographic depiction of tumor vascularity and flow: From in vivo models to clinical applications. J Ultrasound Med 19:55, 2000.
11. Giovagnorio F, Andreoli C, De Cicco ML: Color Doppler sonography of focal lesions of the skin and subcutaneous tissue. J Ultrasound Med 18:89, 1999
12. Paolo Belli, Melania Costantini, Paoletta Mirk, Giulia Maresca, Francesco Priolo, Pasquale Marano. Role of Colour Doppler Sonography in the assessment of Musculoskeletal Soft Tissue Masses. J Ultrasound Med 2000; 19: 823-830.
13. Lagalla R, Iovane A, Caruso G, et al: Color Doppler ultrasonography of soft-tissue masses. Acta Radiol 39:421, 1998.
14. Toprak H, Kiliç E, Serter A, Kocakoç E, Ozgocmen S. Ultrasound and Doppler US in Evaluation of Superficial Soft-tissue Lesions. J Clin Imaging Sci. 2014;4:12. Published 2014 Feb 27. doi:10.4103/2156-7514.127965.
15. Esther Hiu Yee Hung, James Francis Griffith, Alex Wing Hung Ng, Ryan Ka Lok Lee, Domily Ting Yi Lau, and Jason Chi Shun Leung American Journal of Roentgenology 2014 202:6, W532-W540.
16. Morii, T., Kishino, T., Shimamori, N. et al. J Med Ultrasonics (2018) 45: 113. https://doi.org/10.1007/s10396-017-0796-3.
17. Nagano S, Yahiro Y, Yokouchi M, et al. Doppler ultrasound for diagnosis of soft tissue sarcoma: efficacy of ultrasound-based screening score. Radiol Oncol. 2015;49(2):135–140. Published 2015 Mar 25. doi:10.1515/raon-2015-0011.
18. van der Woude H.J., Verstraete K.L., Bloem J.L. (2006) Color Doppler Ultrasound. In: De Schepper A.M., Vanhoenacker F., Gielen J., Parizel P.M. (eds) Imaging of Soft Tissue Tumors. Springer, Berlin, Heidelberg.
19. Shaifali Kaushik, Theodore T. Miller, Levon N. Nazarian, William C. Foster. Spectral Doppler Sonography of Musculoskeletal Soft Tissue Masses. J Ultrasound Med 2003; 22:1333-1336.
20. Bodner G, Schocke MF, Rachbauer F, Seppi K, Peer S, Fierlinger A, Sununu T and Jaschke WR: Differentiation of malignant and benign musculoskeletal tumors: combined color and power Doppler US and spectral wave analysis. Radiology 223: 410-416, 2002.
21. Jo VY and Fletcher CD: WHO classification of soft tissue tumours: an update based on the 2013 (4th) edition. Pathology 46: 95-104, 2014.
22. Drapé JL: Advances in magnetic resonance imaging of musculoskeletal tumours. Orthop Traumatol Surg Res 99 (Suppl 1): S115-S123, 2013.
23. Landa J and Schwartz LH: Contemporary imaging in sarcoma. Oncologist 14: 1021-1038, 2009.
24. Iwamoto Y: Diagnosis and treatment of soft tissue tumors. J Orthop Sci 4: 54-65, 1999.
25. ESMO/European Sarcoma Network Working Group: Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 23 (Suppl 7): vii92-vii99, 2012
26. Metheny-Barlow LJ and Li LY: The enigmatic role of angiopoietin-1 in tumor angiogenesis. Cell Res 13: 309-317, 2003
27. Ozbek SS, Arkun R, Killi R, et al: Image-directed color Doppler ultrasonography in the evaluation of superficial solid tumors. J Clin Ultrasound 23:233, 1995.
28. Lange TA, Austin CW, Seibert JJ, Angtuaco TL and Yandow DR: Ultrasound imaging as a screening study for malignant softtissue tumors. J Bone Joint Surg Am 69: 100-105, 1987.
29. Chiou HJ, Chou YH, Chiu SY, wang Hk, Chen wM, Chen TH and Chang CY: Differentiation of benign and malignant superficial soft-tissue masses using grayscale and color doppler ultrasonography. J Chin Med Assoc 72: 307-315, 2009.
30. OEBISU, N., HOSHI, M., IEGUCHI, M., TAKADA, J., IWAI, T., OHSAWA, M., & NAKAMURA, H. (2014). Contrast-enhanced color Doppler ultrasonography increases diagnostic accuracy for soft tissue tumors. Oncology Reports, 32(4), 1654–1660.doi:10.3892/or.2014.3378.
31. Bradley J. Carra, Liem T. Bui-Mansfield, Seth D. O'Brien, and Dillon C. Chen American Journal of Roentgenology 2014 202:6, 1281-1290 Sonography of Musculoskeletal Soft-Tissue Masses: Techniques, Pearls, and Pitfalls.