ISSN 2706-6819 Vol.5, Issue 3: 28-33, DOI: 10.25236/IJFM.2023.050305

Advances in the application of contrast-enhanced ultrasound in the differential diagnosis of benign and malignant cervical lymph nodes

Jianglong Liu, Reyilai Abudukeremu, Maimaitituxun Tuerdi*

Department of Oral and Maxillofacial Trauma and Orthognathic Surgery, First Affiliated Hospital (Stomatological Hospital) of Xinjiang Medical University, Urumqi, 830054, China
**Corresponding author: maimaitituxun@aliyun.com*

Abstract: *The accurate diagnosis and differential diagnosis of cervical lymph node lesions are very important for making scientific diagnosis and treatment strategy and evaluating the prognosis of the disease. Contrast-enhanced ultrasound (CEUS) can continuously observe the microcirculation and blood flow perfusion of lymph nodes, and significantly improve the accuracy of diagnosis of cervical lymph nodes, it has been gradually applied to localize the sentinel lymph node, guide biopsy, evaluate the treatment effect of lymph node and molecular imaging. This article reviews the recent advances in the application of CEUS in the diagnosis of benign and malignant cervical lymph nodes.*

Keywords: *contrast-enhanced ultrasound, cervical lymph nodes, differential diagnosis*

The evaluation of cervical lymph nodes plays an important role in the diagnosis and treatment of tumors, especially in the proper management of head and neck tumors, it is related to the tumor stage, whether to operate, the range of operation, whether to carry out postoperative radiotherapy and other treatment, and the evaluation of prognosis. Conventional ultrasound is a practical imaging evaluation method for cervical lymph nodes. After more than 30 years of experience, its diagnostic efficiency can reach above 75%. CEUS is a new imaging method developed on the basis of conventional ultrasound. Microbubbles enter the blood circulation of target organs to form a new acoustic interface and enhance ultrasonic backscatter, it can better display the micro-vessels and capillary in the lymph nodes, and dynamically observe the blood perfusion in the lymph nodes in real time, so as to provide more abundant diagnostic information for the judgment of the nature of the cervical lymph nodes. In this paper, we reviewed the literature of recent years, in order to describe the methods and effects of CEUS in the evaluation of diseases of cervical lymph nodes.

1. The principle of CEUS and the feasibility of differentiating benign and malignant cervical lymph nodes

Because of the poor backscattering ability of blood cells, many new acoustic interfaces can be formed by adding gas with large acoustic impedance difference to the blood, which can enhance the intensity of ultrasonic backscattering. The microbubbles commonly used in contrast-enhanced ultrasound of cervical lymph nodes always flow in the blood circulation system without exudation outside the blood vessels, and the microbubbles contract and expand under the action of alternating sound pressure in the sound field, thus producing resonance, the backscattering intensity of microbubbles is stronger. The first generation of ultrasound contrast agents have a thick outer shell and poor resonant capacity [1], requiring imaging at a high mechanical index, coupled with poor stability, and microbubbles tend to rupture before reaching the microvascular network, it cannot reflect the microcirculation in the node effectively [2]. The main role of levovist is to enhance color or energy doppler blood flow signals. Benign and malignant lymph nodes have different patterns of vascular distribution. Benign lymph nodes are supplied by 1-2 lymphatic portal arterioles, which branch out from the arterioles at the lymphatic portal. Metastatic lymph node cancer tissues first enter the lymph node via an afferent lymphatic vessel, grow centripetal, and secrete angiogenesis-inducing factors that stimulate neovascularization [3] . Levovist can obtain relatively complete information of the distribution of blood vessels in lymph nodes, which can help to judge the nature of lymph nodes.

The second generation of ultrasound contrast agents have high bubble stability and good shell resonance, allowing continuous harmonic signals to be generated without breaking at low mechanical

ISSN 2706-6819 Vol.5, Issue 3: 28-33, DOI: 10.25236/IJFM.2023.050305

indices, thereby obtaining real-time images [4] , it is used to observe the microvascular perfusion in lymph nodes. Tumor tissue has specific microcirculation characteristics. The tumor tissue growing in the lymph node damages the local microvessel, although it can continuously induce the new blood vessel and form the microvascular network, but the microcirculation is not well developed, showing low efficiency and relatively insufficient function, in addition, neoplastic blood vessels were mainly distributed in the marginal area of active tumor growth, while they were prone to necrosis in the central area of the tumor. Therefore, the second generation microbubbles can provide valuable information for the diagnosis of lymph node diseases.

2. The history of CEUS was used to differentiate benign and malignant cervical lymph nodes

Conventional ultrasound techniques differentiate cervical lymph node disease by measuring or observing the characteristics of lymph node volume, aspect ratio, hilum, internal echo, border and vascular distribution pattern [5] . Color or power doppler ultrasound is not sensitive to low velocity and blood flow, and cannot show the tiny blood vessels in lymph nodes well, It is difficult to display blood flow signal in small or deep lymph nodes, and it is often interfered by color artifacts in lymph nodes near great vessels, which limits the differential diagnosis of benign and malignant cervical lymph nodes by conventional ultrasound. In addition, it is difficult for conventional ultrasound to detect small infiltrates in lymph nodes less than 5 mm in diameter [6] . Therefore, a more effective imaging method is needed to supplement the deficiency of conventional ultrasound. Since the early 1990s, great progress has been made in the development of ultrasound contrast agents. The first and second generation of ultrasound contrast agents have been developed one after another, which lays a foundation for the study of cervical lymph node diseases by ultrasound contrast agents. Ultrasound contrast agent can be injected through vein and tissue, the latter includes three ways: subcutaneous, submucosa and parenchyma. The study of cervical lymph node usually adopts peripheral vein injection. Moritz et al.[7]studied the blood flow patterns of enlarged cervical lymph nodes in patients withhead and neck cancer using sonographic imaging. The results showed that the sensitivity and specificity for the diagnosis of metastatic lymph nodes were 100% and 98%, respectively, and 28% of the lymph nodes showed only blood vessels after angiography. However, Schulte-altedorneburg et al.[8] showed that although lysophane can improve the blood flow signal of superficial lymph nodes, it cannot improve the diagnostic accuracy of benign and malignant diseases. This conclusion may be due to the small sample size: 27 malignant lymph nodes, only 5 benign lymph nodes, and the increase of color artifacts after angiography, which affect the identification of lymph node blood flow characteristics. Rubaltelli et al.[2]used sonovue to analyze blood perfusion in suspected malignant superficial lymph nodes to reflect intranodal blood perfusion in a post-contrast enhanced manner, the results showed that the sensitivity and specificity for the diagnosis of benign and malignant lymph nodes were 92% and 93% , respectively. In malignant lymph nodes, the false-negative cases were all lymphomas, so the sensitivity of lymph node metastasis was 100%, which is consistent with the previous conclusion of Moritz et al.[7]Rubaltelli et al. [9] used sonovue to study superficial lymph node blood perfusion using quantitative analysis of CEUS, a technique that converts the echo intensity of each pixel on an image into a numerical value, the numerical values are rendered as color images by specific software. The closer the color image is to red, the greater the numerical value, that is, the greater the intensity, the closer the blue color image is to the numerical value, that is, the lower the intensity. According to the color distribution, the observer can delineate the region of interest and obtain the time-intensity curve, and differentiate the benign and malignant lymph nodes by analyzing the parameters. Rubaltelli et al. [10]used sonovue to assess microinfiltrative foci in the cortex of superficial lymph nodes in patients with heterogeneous cortical thickening (2 times thinner at the thickest sites) and no other malignant manifestations on routine ultrasound, the results showed that the sensitivity and specificity of sonovue were 100% and 93.5% .

3. The performance of CEUS of benign and malignant cervical lymph nodes

3.1 Normal or reactive lymph node hyperplasia of the cervical

The pattern of blood vessel distribution was mainly portal blood flow, which showed radiating branches of blood flow signal and its emission in central lymphatic hilum, and the enhancement pattern of lymph nodes was homogeneous and significantly enhanced, the appearance of contrast media was central enhancement and peripheral enhancement, and the contrast media entered the peak with high enhancement of the whole lymph node and then subsided[11] . The time-intensity curve shows a steep rise, then a rapid decline and then a slow decline at the peak [12] . In the study of Zhang Y et al.[3], in addition

ISSN 2706-6819 Vol.5, Issue 3: 28-33, DOI: 10.25236/IJFM.2023.050305

to homogeneous and significant enhancement of the benign lymph nodes, the parenchymal irregular low or non-perfused region of the perihilum was also found, the reason may be that adipose tissue infiltration leads to lymphatic tissue compression to the margins, and the medullary adipose tissue of the lymph nodes may increase with age [6] . In addition, very few inflammatory lymph nodes exhibit filling defects [2,3] , which may be associated with fibrosis.

3.2 Metastatic lymph nodes in the cervical

The distribution of blood vessels was peripheral blood flow or mixed blood flow. The peripheral blood flow showed the signal of blood flow around lymph node and its perforating branch. The enhancement patterns of metastatic lymph nodes were inhomogeneous enhancement, and the radiography showed marked enhancement from the periphery, but the distribution was uneven. Low or non-perfusion areas with different sizes were seen in the radiography, and then slowly subsided. The line of time-intensity curve is steep ascending branches, reached the peak of continuous slow decline, peak intensity is less than benign or lymphoma lymph nodes. The pathological control showed that the low perfusion area in the node was tumor tissue and the non-perfusion area was necrotic area. Some metastatic lymph nodes showed weak enhancement or lack of enhancement. When Rubaltelli et al. [10]used sonovue to study microinvasive lesions, they specified that the first 5 min after the contrast agent entered the lymph node was the arterial phase, and the first 6-20 min was the parenchymal phase, and when the arterial phase was found, the perfusion of the infiltrated area was lower than that of the surrounding cortex, showing as a low-enhanced area in the significantly enhanced lymph nodes, especially in the parenchymal phase.

3.3 Tuberculous lymph nodes in the cervical

At present, there are relatively few studies on CEUS of tuberculous lymph nodes in the cervical, and Wen BP et al. [13]reported that rim enhancement combined with central honeycomb-like or segmented-like enhancement, it may be a characteristic feature of CEUS in cervical lymph node tuberculosis. The reason for this is that when mycobacterium tuberculosis enters the lymph nodes and is engulfed by macrophages, it induces a delayed-type allergic reaction, causing caseous necrosis of cells, causing tissue destruction and formation of necrotic areas. Tuberculous lymph nodes can also appear as non-enhancing lymph nodes, often in small lymph nodes, because of extensive necrosis within the node. CEUS of tuberculous lymph nodes is sometimes difficult to differentiate from malignant lymph nodes, and should be combined with a comprehensive diagnosis such as spectrum dopler, the intranodal blood flow pulsatility index < 1.5 or can help to differentiate tuberculous lymph nodes from metastatic carcinomas [14]. If necessary, fine needle aspiration biopsy guided by ultrasound can be performed in the enhanced defect area, and the results are usually satisfactory.

3.4 Lymphoma of the cervical

The distribution pattern of blood vessels is mostly portal blood flow, which may be due to the fact that the lymphomas originate from the cells in the node and grow from the center to the periphery in a centrifugal manner, so the blood vessels of the lymphomas are similar to those of the normal lymph nodes. Giovagnorio et al. [15] reported hilar flow in 90 of 96 lymphoma lymph nodes, the remaining 6 showed peripheral or mixed flow and all were highly malignant subtypes, these results suggest that the distribution of blood vessels in lymph nodes may be related to pathological subtypes. Nakase et al. [16] used sonographic imaging to study vascular distribution patterns in different subtypes of lymphoma, and the results showed features of portal-type blood flow or B-cell lymphoma, whereas avascular type was seen in lymphocyte-depleted lymphoma, but its sample size is small and pathological subtype is not comprehensive. In addition, the lymph nodes of lymphoma had their own unique enhancement patterns: the perfusion areas were diffusely distributed with small dots in the early stage, then the dots fused with each other, and the lymph nodes in the venous stage showed significant homogeneous enhancement. The time-intensity curve showed that the ascending branch was steep and straight, and the peak time was shorter and the peak intensity was higher than that of benign or metastatic lymph nodes. The enhanced features of the above-mentioned lymphomas may be related to the abnormal dilatation of small arteries in the nodes.

ISSN 2706-6819 Vol.5, Issue 3: 28-33, DOI: 10.25236/IJFM.2023.050305

4. CEUS, contrast-enhanced CT and dynamic contrast-enhanced MRI in the differential diagnosis of benign and malignant cervical lymph nodes

Contrast medium of contrast-enhanced CT and dynamic contrast-enhanced MRI are iodine-containing contrast medium and paramagnetic contrast medium respectively. The former can enhance image density contrast of X-ray, while the latter can shorten the relaxation time of T1 and T2, affect signal intensity to enhance image contrast. They are different from the above ultrasound contrast agents in the metabolism process in vivo, after peripheral intravenous injection, they quickly reach equilibrium in the extracellular space between the blood vessel and the outside of the blood vessel, that is to say, they enter the equilibrium period. Unzurrunzaga E I et al. [17] performed enhanced CT analysis of cervical lymph nodes in 98 patients with pharyngeal and laryngeal tumors, the results showed a sensitivity of 82.0% and a specificity of 85.7% for the diagnosis of metastatic lymph nodes based on rim enhancement or central necrosis, which is consistent with other studies[18,19]. Fischbein NJ et al.[20] studied MRI dynamic enhancement parameters, including peak time, peak enhancement rate, and maximum enhancement rate, in 68 cervical lymph nodes from 21 squamous-cell carcinoma patients, the results showed that the peak time of lymph node metastasis was longer than that of normal lymph node, the peak enhancement rate was lower and the maximum enhancement rate was lower. When Hu Z et al.[21] analyzed the enlarged lymph nodes in the neck of 46 patients, they found that metastatic lymph nodes usually showed homogeneous thin ring, irregular or serrated enhancement on dynamic contrast-enhanced MRI, and no enhancement was found in the necrotic foci, the diagnostic accuracy of dynamic contrast-enhanced MRI for metastatic lymph nodes was 76.1% . The results showed that the manifestations of lymph node diseases on contrast-enhanced ultrasonography, contrast-enhanced CT and dynamic contrast-enhanced MRI were similar, CEUS is more effective than contrast-enhanced CT and dynamic contrast-enhanced MRI in the differential diagnosis of benign and malignant cervical lymph nodes.[17-19] However, because a single injection of contrast agent can only study one resection, plane and other factors, CEUS has limitations in the overall assessment of the disease, such as the source of the primary tumor focus, tumor stage judgment.Contrast-enhanced CT is necessary for screening deep cervical lymph nodes such as retropharyngeal space lymph nodes. Therefore, contrast-enhanced CT can be used to detect suspected malignant cervical lymph nodes in patients with head and neck tumors, CEUS may be performed on the screened lymph nodes to obtain further diagnostic information. Others have found that the combination of CEUS and dynamic contrast-enhanced MRI is also an effective diagnostic tool[22] .

5. Conclusion

CEUS provides more information from perfusion level for the evaluation of cervical lymph nodes and is of high diagnostic value. Although it has some limitations, such as the low mechanical index of the second-generation contrast agent, the image resolution is affected, but the development prospect of contrast-enhanced ultrasound is encouraging. In particular, some new techniques, such as needle-localization-guided techniques, help to guide biopsy material through contrast-enhanced ultrasound to improve diagnostic rates of needle biopsies [23] . Mauri G et al.[24] compared the results of CEUS-guided and conventional ultrasound-guided cervical tuberculous lymph node puncture, and concluded that CEUS increased the rate of complete biopsy and pathological diagnosis. Furthermore, CEUS can reduce the rate of lymph node aspiration, and a growing number of scholars advocate fine-needle biopsy of lymph nodes with local cortical thickening in patients with tumours[25] , but because of human resource and economic constraints, needle biopsies of all suspected malignant lymph nodes are difficult to perform. Whereas multiple studies[26,27] have shown that CEUS has a high sensitivity for the diagnosis of lymph node metastases, up to 100% , and that it can screen lymph nodes for unnecessary biopsy by CEUS, thus greatly reduce the number of lymph nodes to be biopsied. In addition to intravenous ultrasound contrast agents for the observation of superficial lymph nodes, in recent years, many scholars [28,29] have used a novel second-generation contrast agent called Sonazoid by intratissue injection, detecting sentinel lymph node in animal models. Sonazoid also has tissue-specific characteristics, it can be engulfed by the reticuloendothelial system in lymph nodes, thus changing the echo intensity of lymph nodes. Goldberg et al.[30] subcutaneously injected a Sonazoid probe around a porcine malignant melanoma and observed the sentinel lymph node, and injected a 99TcM isotope at the same site for a comparative study, the results showed that the sensitivity of CEUS was 81.8% , higher than that of isotope sentinel lymph node 63.2%. The application of these new techniques in the evaluation of cervical lymph nodes needs further study.

ISSN 2706-6819 Vol.5, Issue 3: 28-33, DOI: 10.25236/IJFM.2023.050305

References

[1] Correas J M, Bridal L, Lesavre A, et al. Ultrasound contrast agents: properties, principles of action, tolerance, and artifacts [J]. European radiology, 2001, 11(8): 1316-1328.
[2] Rubaltelli L, Khadivi Y, Tregnaghi A, et al. Evaluation of lymph node perfusion using continuous mode harmonic ultrasonography with a second-generation contrast agent [J]. Journal of ultrasound in medicine, 2004, 23(6): 829-836.
[3] Zhang Y, Zhang X, Li J, et al. Contrast-enhanced ultrasound: a valuable modality for extracapsular extension assessment in papillary thyroid cancer [J]. European Radiology, 2021, 31(7): 4568-4575.
[4] Kapetas P, Clauser P, Woitek R, et al. Quantitative multiparametric breast ultrasound: application of contrast-enhanced ultrasound and elastography leads to an improved differentiation of benign and malignant lesions [J]. Investigative radiology, 2019, 54(5): 257.
[5] Ahuja A, Ying M. An overview of neck node sonography [J]. Investigative radiology, 2002, 37(6): 333-342.
[6] Chen X, Zhang XJ, Chen JY, et al.The application value of manual biopsy combined with ultrasonography in the diagnosis of superficial enlarged lymph nodes [J]. Chin J Ultra Med, 2018, 34(4):331-333.
[7] Moritz J D, Ludwig A, Oestmann J W. Contrast-enhanced color Doppler sonography for evaluation of enlarged cervical lymph nodes in head and neck tumors[J]. American Journal of Roentgenology, 2000, 174(5): 1279-1284.
[8] Schulte-Altedorneburg G, Demharter J, Linné R, et al. Does ultrasound contrast agent improve the diagnostic value of colour and power Doppler sonography in superficial lymph node enlargement?[J]. European journal of radiology, 2003, 48(3): 252-257.
[9] Rubaltelli L, Corradin S, Dorigo A, et al. Automated quantitative evaluation of lymph node perfusion on contrast-enhanced sonography[J]. American Journal of Roentgenology, 2007, 188(4): 977-983.
[10] Rubaltelli L, Beltrame V, Tregnaghi A, et al. Contrast-enhanced ultrasound for characterizing lymph nodes with focal cortical thickening in patients with cutaneous melanoma[J]. American Journal of Roentgenology, 2011, 196(1): W8.
[11] Zhao D, Yang GY, He Ning, et al. Contrast-enhanced ultrasonography for evaluation of cervical lymph node tuberculosis [J]. Chin J Ultra Med, 2015, 31:683-686.
[12] Luo Z Y, Hong Y R, Yan C X, et al. Utility of quantitative contrast-enhanced ultrasound for the prediction of lymph node metastasis in patients with papillary thyroid carcinoma[J]. Clinical Hemorheology and Microcirculation, 2022, 80(1): 37-48.
[13] Wen BP, Yang GY, Xu JP, et al. Role of contrast -enhanced ultrasound in assessment of laser ablation of tuberculous cervical lymphadenitis[J]. Chin J Med Ultrasound (Electronic Edition), 2019, 16(1): 16.
[14] Ying M, Ahuja A, Brook F. Accuracy of sonographic vascular features in differentiating different causes of cervical lymphadenopathy[J]. Ultrasound in medicine & biology, 2004, 30(4): 441-447.
[15] Giovagnorio F, Galluzzo M, Andreoli C, et al. Color Doppler sonography in the evaluation of superficial lymphomatous lymph nodes[J]. Journal of ultrasound in medicine, 2002, 21(4): 403-408.
[16] Nakase K, Yamamoto K, Hiasa A, et al. Contrast-enhanced ultrasound examination of lymph nodes in different types of lymphoma[J]. Cancer Detection and Prevention, 2006, 30(2): 188-191.
[17] Unzurrunzaga E I, Angulo M G, Arechaga L V, et al. Predictive ability of the CT to evaluate cervical lymph nodes in head and neck tumours[J]. Acta Otorrinolaringologica (English Edition), 2011, 62(6): 443-447.
[18] Magdy G , Belal F , Elmansi H . Rapid microwave-assisted synthesis of nitrogen-doped carbon quantum dots as fluorescent nanosensors for the spectrofluorimetric determination of palbociclib: application for cellular imaging and selective probing in living cancer cells[J]. RSC Advances, 2023, 13.
[19] Ding Z, Deng C, Wang Z, et al. Comparison of contrast-enhanced ultrasound and contrast-enhanced computed tomography for the diagnosis of cervical lymph node metastasis in squamous cell carcinoma of the oral cavity[J]. International Journal of Oral and Maxillofacial Surgery, 2021, 50(3): 294-301.
[20] Fischbein NJ, Noworolski SM, Henry RG, et al. Assessment of metastatic cervical adenopathy using dynamic contrast-enhanced MR imaging[J]. AJNR Am J Neuroradiol, 2003, 24(3): 301-311.
[21] Hu Z, Cheng X, Li J, et al. Preliminary study of real-time three-dimensional contrast-enhanced ultrasound of sentinel lymph nodes in breast cancer[J]. European Radiology, 2020, 30(3): 1426-1435.
[22] Wendl C M, Müller S, Meier J, et al. High resolution contrast-enhanced ultrasound and 3-tesla dynamic contrast-enhanced magnetic resonance imaging for the preoperative characterization of cervical lymph nodes: first results[J]. Clinical hemorheology and microcirculation, 2012, 52(2-4): 153-166.
[23] Spartalis E, Karagiannis S P, Plakopitis N, et al. Percutaneous laser ablation of cervical metastatic

ISSN 2706-6819 Vol.5, Issue 3: 28-33, DOI: 10.25236/IJFM.2023.050305

lymph nodes in papillary thyroid carcinoma: clinical efficacy and anatomical considerations [J]. Expert Review of Medical Devices, 2021, 18(1): 75-82.
[24] Mauri G, Cova L, Tondolo T, et al. Percutaneous laser ablation of metastatic lymph nodes in the neck from papillary thyroid carcinoma: preliminary results [J]. The Journal of Clinical Endocrinology & Metabolism, 2013, 98(7): E1203-E1207.
[25] Cui Q, Yin S, Fan Z H, et al. Diagnostic Value of Contrast-Enhanced Ultrasonography and Time-Intensity Curve in Differential Diagnosis of Cervical Metastatic and Tuberculous Lymph Nodes[J]. Journal of Ultrasound in Medicine, 2018, 37(1): 83-92.
[26] Clevert D A, D'Anastasi M, Jung E M. Contrast-enhanced ultrasound and microcirculation: efficiency through dynamics-current developments [J]. Clinical hemorheology and microcirculation, 2013, 53(1-2): 171-186.
[27] David E, Cantisani V, De Vincentiis M, et al. Contrast-enhanced ultrasound in the evaluation of parotid gland lesions: an update of the literature[J]. Ultrasound, 2016, 24(2): 104-110.
[28] Rahman M A, Sultana N, Uddin M W, et al. The Role of High Resolution Ultrasonography to Differentiate Between Benign and Malignant Cervical Lymph Nodes in Oral Squamous Cell Carcinoma [J]. Update Dental College Journal, 2017, 7(2): 19-27.
[29] Averkiou M, Powers J, Skyba D, et al. Ultrasound contrast imaging research [J]. Ultrasound quarterly, 2019, 19(1): 27-37.
[30] Goldberg B B, Merton D A, Liu J B, et al. Contrast-enhanced ultrasound imaging of sentinel lymph nodes after peritumoral administration of Sonazoid in a melanoma tumor animal model[J]. Journal of Ultrasound in Medicine, 2018, 30(4): 441-453.