综述

Progresses of CEUS in diagnosis of breast cancers

WANG Yunyue[1], RUAN Litao[1*], REN Yu[2], SHANG Jing[1], DANG Ying[1]
(1. Department of Ultrasound Medicine, 2. Department of Breast Surgery, the First Affiliated Hospital, Xi'an Jiaotong University, Xi'an 710061, China)

[**Abstract**] CEUS is a pure blood pool imaging depending on the non-linear effect and strong backscatter of gas-filled microbubbles in blood to obtain contrast-enhanced images. With the advantages of displaying tumor microvascular dynamically and intuitively, CEUS has been widely used for diagnosis and evaluating prognosis of breast cancers. CEUS has high sensitivity and specificity in detecting early breast cancers and identifying sentinel lymph nodes, with wide application prospects in assessing the efficacy of neoadjuvant therapy, predicting molecular typing and targeted therapy of breast cancers. The features of CEUS in breast cancers and the relationships with biomarkers, progresses in assessing neoadjuvant therapy and assisting sentinel lymph node biopsy were reviewed in the article.

[**Key words**] Breast neoplasms; Ultrasonography; Contrast media; Molecular typing; Neoadjuvant therapy; Sentinel lymph node
DOI: 10.13929/j.1003-3289.201711122

CEUS 诊断乳腺癌研究进展

王云月[1],阮骊韬[1*],任 予[2],商 静[1],党 莹[1]
(1.西安交通大学第一附属医院超声影像科,2.乳腺外科,陕西 西安 710061)

[**摘 要**] CEUS是纯血池显像,利用血液中含气微泡造影剂在声场中的非线性效应和强烈的背向散射获得对比增强图像,可动态直观地显示肿瘤微血管,已广泛应用于乳腺癌的诊断和疗效评估。CEUS在检出早期乳腺癌和识别前哨淋巴结方面具有较高敏感度和特异度,在评估新辅助化疗疗效、预测乳腺癌分子分型和辅助乳腺癌靶向治疗领域具有广阔的应用前景。本文对乳腺癌CEUS特点及其与生物标志物的关系、CEUS评价新辅助化疗疗效及辅助前哨淋巴结活检术方面的进展进行综述。

[**关键词**] 乳腺肿瘤;超声检查;造影剂;分子分型;肿瘤辅助疗法;前哨淋巴结
[**中图分类号**] R737.9; R445.1 [**文献标识码**] A [**文章编号**] 1003-3289(2018)04-0633-04

目前,乳腺癌是全球范围内女性最常见的恶性肿瘤[1],居女性癌症死因的第2位[2]。近年来,北美和欧盟等发达地区国家的乳腺癌死亡率已有所降低,而南美洲、非洲和亚洲欠发达国家乳腺癌的发病率及死亡率仍呈上升趋势,这种差距与后者缺乏乳腺癌早期筛查手段和先进的诊疗方法有关[1,3-4]。尽管乳腺钼靶摄影是首选的乳腺癌筛查方法[5],但我国女性乳腺致密型居多,影响钼靶摄影的诊断效能。常规超声检查对检出乳腺癌有重要价值,但其特异度较低[6]。CEUS是一种纯血池显像技术,可安全、高效、实时动态地显示脏器及肿瘤内部的微灌注情况[7],在诊断乳腺癌、检出前哨淋巴结(sentinel lymph node, SLN)[8-10]、评估新辅助化疗疗效[11-12]及辅助乳腺癌靶向治疗[13]等方面的作用逐渐凸显。本文就乳腺癌CEUS特点、CEUS与生物标志物的关系、评价新辅助化疗疗效和辅助前哨淋巴结活检术(sentinel lymph node biopsy, SLNB)等方面的研究进展进行综述。

[**基金项目**] 陕西省重点研发计划一般项目(2017SF-132)。
[**第一作者**] 王云月(1992—),女,陕西宝鸡人,在读硕士。研究方向:乳腺CEUS。E-mail: wangyunyue0000@stu.xjtu.edu.cn
[**通信作者**] 阮骊韬,西安交通大学第一附属医院超声影像科,710061。E-mail: rlt555@mail.xjtu.edu.cn
[**收稿日期**] 2017-11-22 [**修回日期**] 2018-01-29

1　概述

CEUS 是通过向周围静脉内注射直径与红细胞相似的气体微泡造影剂，利用气体较强的散射性及与人体组织不同的声学特性，增大血流或病变与相邻组织间的声阻抗差异，从而获得反差较大的声像图。目前我国常用造影剂为 SonoVue(声诺维)。CEUS 为纯血池显像，其微泡造影剂直径较大(约2.5 μm)，可进入肿瘤微毛细血管，但不能透过血管内皮间隙弥散进入周围组织[14]。

2　乳腺癌 CEUS 特点

2.1　定性诊断　乳腺癌 CEUS 多表现为不均匀增强，达峰时呈高增强，病灶范围较增强前扩大，边界不清，边缘模糊呈“蟹足样”或“放射状”[10,15-16]。Liu 等[15]认为增强是否均匀、病灶范围有无扩大和增强程度是鉴别乳腺良、恶性病变的重要因素；恶性病变多表现为不均匀、向心性增强，而良性病变多表现为均匀性、离心性增强。Zhao 等[17]观察不同大小乳腺癌的增强模式，认为最大径＞20 mm 的乳腺癌以非均匀性增强模式为主，而直径≤20 mm 者以均匀性增强模式为主。另有研究[18]表明，穿支血管常见于高级别肿瘤；根据肿瘤内部充盈缺损诊断乳腺癌的特异度较高[19]。

2.2　定量诊断　采用时间-强度曲线(time-intensity curve，TIC)定量分析法，可获得 CEUS 定量参数，包括上升时间(rise time，RT)、达峰时间(time to peak，TTP)、峰值强度(peak intensity，PI)、平均渡越时间(mean transit time，MTT)和 ROC 曲线下面积(area under curve，AUC)等。Ji 等[18]研究 102 例浸润性导管癌，发现浸润性导管癌中，高级别肿瘤(Ⅲ级)的 RT 和 TTP 均大于低级别肿瘤(Ⅰ级和Ⅱ级)。Yuan 等[20]发现乳腺良恶性病灶间 RT、TTP 和 MTT 差异均有统计学意义，良性组和恶性组的 RT 分别为(16.52±4.15)s 和(13.86±3.36)s(P=0.007)，TTP 分别为(19.86±4.87)s 和(16.52±4.85)s(P=0.009)，MTT 分别为(80.55±18.65)s 和(65.16±20.28)s(P=0.006)。Zhao 等[10]发现 PI 诊断乳腺癌的 AUC 为 0.919，诊断效能较高。

3　CEUS 与乳腺癌生物标志物的关系

随着乳腺癌诊疗模式逐渐转向精准医学，根据乳腺癌分子分型进行精准对症治疗成为研究热点。诸多学者致力于观察 CEUS 与乳腺癌生物标志物雌激素受体(estrogen receptor，ER)、孕激素受体(progesterone receptor，PR)、人类表皮生长因子受体2(human epidermal growth factor receptor-2，HER-2)、Ki-67 等的相关性，以期建立对乳腺癌分子分型的预测模型。

研究[17]发现，CEUS 增强后病灶范围增大是 ER(＋)乳腺癌的独立影响因素[回归系数(B)＝1.504，P=0.032]，而穿支血管缺失与 ER(－)乳腺癌有关(B＝1.396，P=0.022)；ER(－)或 PR(－)乳腺癌的肿瘤最大灌注强度(maximum intensity of tumor perfusion，IMAX)高于 ER(＋)或 PR(＋)乳腺癌[18]。Ki-67(＋)的浸润性导管癌较 Ki-67(－)者 RT 更短、IMAX 更高、造影剂廓清速度更慢[18]，灌注缺损也较常见[10]。Her-2(＋)与 Her-2(－)乳腺癌患者 RT、不均匀性增强发生率差异均有统计学意义，这一特点可作为预测 Her-2(＋)分型的因素[18]。对不同 Her-2 表达水平的乳腺癌 CEUS 特点的研究[21]结果表明，HER-2 过度表达与造影剂分布、穿支血流、增强后病灶范围增大和灌注缺损有关；且与 HER-2(－)组相比，HER-2 过表达组 TIC 上升支斜率(K)更大、PT 更短、下降支平坦、造影剂廓清时间延迟及 AUC 较大，而病灶增强程度和 PI 与 HER-2 的表达状态无关。乳腺癌不同 CEUS 增强模式及量化参数与其生物学标志物的表达状态存在一定关系，提示有望通过影像学手段在分子水平对乳腺癌进行观察，从而达到精准诊断和治疗的目的。

4　CEUS 评价乳腺癌新辅助化疗疗效

新辅助化疗是指在乳腺肿瘤手术或放疗前全身应用化疗，以缩小原发灶和(或)转移淋巴结体积，从而达到增加手术机会、保乳或延长患者生存期的治疗方法，现已广泛应用于临床。及时准确评估乳腺癌新辅助化疗的疗效、确定残余肿瘤大小及边界有助于及早调整治疗策略、改善预后[22]，但目前临床缺乏公认的有效评估手段。病理学是评估新辅助化疗的金标准，但存在严重滞后性[23]。MRI 是评估肿瘤新辅助化疗疗效的首选方法，但检查费用昂贵、耗时长，且可能高估或低估残余肿瘤范围[24-25]，难以普遍应用于临床。

CEUS 可获得肿瘤的宏观和微观信息，评价肿瘤新生血管情况，现已用于评价新辅助化疗疗效。Saracco 等[26]发现超声造影剂药物代谢动力学指标改变可反映新辅助化疗后乳腺肿瘤新生血管网的早期改变，区分新辅助化疗后肿瘤纤维化(无增强)与活性残余肿瘤(增强)[27]。新辅助化疗后肿瘤组织 CEUS 多表现为缓慢强化或无强化，可能是由于新辅助化疗的抗血管作用使病灶内的血液灌注减少、肿瘤内血管内皮生长因子聚集减少、新生血管生成受阻所致[11]。

Lee 等[27]认为 CEUS 测量的化疗后肿瘤大小与手术病理所示肿瘤大小的相关性($r=0.75$, $P<.001$)优于 MRI 与手术病理的相关性($r=0.42$, $P=0.095$),而在预测乳腺癌病理学完全缓解(pathological complete response, pCR)方面,二者准确率相同,均为 75.0%。Amioka 等[11]发现 CEUS 评估乳腺癌新辅助化疗后 pCR 的敏感度、特异度及准确率分别为 95.7%、77.5%及 84.1%,高于增强 MRI 和 PET/CT;PI 预测乳腺癌新辅助化疗后 pCR 的最佳临界值为 25.65 dB,AUC 为 0.902($P<0.001$)。CEUS 联合其他超声技术评估新辅助化疗疗效的效能更佳。Nam 等[28]将 CEUS 与次谐波成像技术结合,利用次谐波辅助压力评估技术(subharmonic aided pressure estimation, SHAPE)评估新辅助化疗对乳腺癌的疗效,化疗后缓解者肿瘤组织的次谐波信号增加幅度大于部分或无缓解者。

5 CEUS 辅助 SLNB

SLN 是指最早接受肿瘤区域淋巴引流和发生肿瘤转移的第一站淋巴结,可反映淋巴引流区域的肿瘤状况,对判断肿瘤分期至关重要。常用 SLN 检测方法有蓝染法、^{99m}Tc 标记的放射性同位素法及二者联合应用,但均存在侵袭性和放射性[29]。CEUS 实时无创、无辐射、无污染,有望成为临床定位和定性诊断 SLN 的新方法。

Rautiainen 等[30]建立猪黑色素瘤模型,通过皮下注射超声造影剂实时显示 SLN 和引流淋巴管,认为该方法优于核素淋巴显像。Matsuzawa 等[31]通过静脉注射造影剂 Sonazoid,发现 CEUS 诊断乳腺癌腋窝 SLN 转移的准确率(90.6%)高于增强 CT 及彩色多普勒超声;经乳晕注射 Sonazoid 造影剂后行 CEUS,其诊断 SLN 转移的效能与 CT 淋巴系统造影法及靛蓝胭脂红法相似。一项 Meta 分析[32]发现 CEUS 对乳腺癌 SLN 转移的诊断效能较高,其合并敏感度、特异度、阳性似然比及阴性似然比分别为 0.80、0.94、6.28 和 0.218,诊断比值比为 49.10,AUC 为 0.937,且其准确率不受造影剂(SonoVue)注射方式的影响。研究[9,33]表明,SLNB 与腋窝淋巴结清扫术(axillary lymph node dissection, ALND)的诊断准确率相似,且前者创伤小,已成为判断乳腺癌腋窝淋巴结转移情况的首选方法。Shimazu 等[34]经乳晕注射 Sonazoid,对临床触诊及影像学检查淋巴结阴性的乳腺癌患者行 CEUS,结果表明该方法对 SLN 的检出率为 98%(98/100),与 Sever 等[35-36]报道的检出率相似;且 CEUS 与蓝染法、放射性胶体法及二者联合使用诊断 SLN 转移的符合率为 100%,提示 CEUS 有助于识别 SLN 并辅助 SLNB,可提高术前乳腺癌临床分期的准确率。

[参考文献]

[1] Harbeck N, Gnant M. Breast cancer. Lancet, 2017, 389(10074):1134-1150.

[2] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer, 2015,136(5):E359-E386.

[3] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin, 2015,65(2):87-108.

[4] Malvezzi M, Carioli G, Bertuccio P, et al. European cancer mortality predictions for the year 2016 with focus on leukaemias. Ann Oncol, 2016,27(4):725-731.

[5] Fan L, Goss PE, Strasser-Weippl K. Current status and future projections of breast cancer in Asia. Breast Care (Basel), 2015, 10(6):372-378.

[6] Meuwly JY. Ultrasound for breast cancer screening: An effective tool in a personalized screening. Praxis (Bern 1994), 2015,104(25):1399-1404.

[7] 何佳,冉海涛.超声造影在乳腺肿瘤诊断中的应用价值.临床超声医学杂志,2017,19(7):471-473.

[8] 陕泉源,罗佳,梁瑾瑜,等.超声造影鉴别诊断乳腺良恶性肿瘤.中国医学影像技术,2015,31(7):1045-1048.

[9] 毕世玥,冉海涛,张群霞,等.CEUS 联合染料法在乳腺癌前哨淋巴结活检术中的应用.中国介入影像与治疗学,2016,13(3):142-145.

[10] Zhao YX, Liu S, Hu YB, et al. Diagnostic and prognostic values of contrast-enhanced ultrasound in breast cancer: A retrospective study. Onco Targets Ther, 2017,10:1123-1129.

[11] Amioka A, Masumoto N, Gouda N, et al. Ability of contrast-enhanced ultrasonography to determine clinical responses of breast cancer to neoadjuvant chemotherapy. Jpn J Clin Oncol, 2016,46(4):303-309.

[12] 张萌璐,马步云.乳腺癌新辅助化疗前后超声造影表现.中国介入影像与治疗学,2015,12(1):52-55.

[13] Jiang Q, Hao S, Xiao X, et al. Production and characterization of a novel long-acting Herceptin-targeted nanobubble contrast agent specific for Her-2-positive breast cancers. Breast Cancer, 2016,23(3):445-455.

[14] Della-Longa S, Arcovito A. Structural and functional insights on folate receptor α (FRα) by homology modeling, ligand docking and molecular dynamics. J Mol Graph Model, 2013, 44:197-207.

[15] Liu J, Gao YH, Li DD, et al. Comparative study of contrast-enhanced ultrasound qualitative and quantitative analysis for identifying benign and malignant breast tumor lumps. Asian Pac J Cancer Prev, 2014,15(19):8149-8153.

[16] Wang X, Xu P, Wang Y, et al. Contrast-enhanced ultrasonographic findings of different histopathologic types of breast cancer. Acta Radiol, 2011,52(3):248-255.

[17] Zhao LX, Liu H, Wei Q, et al. Contrast-enhanced ultrasonography features of breast malignancies with different sizes: Correlation with prognostic factors. Biomed Res Int, 2015,2015:613831.

[18] Ji CL, Li XL, He YP, et al. Quantitative parameters of contrast-enhanced ultrasound in breast invasive ductal carcinoma: The correlation with pathological prognostic factors. Clin Hemorheol Microcirc, 2017,66(4):333-345.

[19] Du J, Wang L, Wan CF, et al. Differentiating benign from malignant solid breast lesions: Combined utility of conventional ultrasound and contrast-enhanced ultrasound in comparison with magnetic resonance imaging. Eur J Radiol, 2012, 81(12): 3890-3899.

[20] Yuan Z, Quan J, Zhang Y, et al. Diagnostic value of contrast-enhanced ultrasound parametric imaging in breast tumors. J Breast Cancer, 2013,16(2):208-213.

[21] Wang XY, Hu Q, Fang MY, et al. The correlation between HER-2 expression and the CEUS and ARFI characteristics of breast cancer. PLoS One, 2017,12(6):e0178692.

[22] von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol, 2012,30(15):1796-1804.

[23] Fisher ER, Wang J, Bryant J, et al. Pathobiology of preoperative chemotherapy: Findings from the National Surgical Adjuvant Breast and Bowel (NSABP) protocol B-18. Cancer, 2002,95(4):681-695.

[24] Kim HJ, Im YH, Han BK, et al. Accuracy of MRI for estimating residual tumor size after neoadjuvant chemotherapy in locally advanced breast cancer: Relation to response patterns on MRI. Acta Oncol, 2007,46(7):996-1003.

[25] Lobbes M, Prevos R, Smidt M. Response monitoring of breast cancer patients receiving neoadjuvant chemotherapy using breast MRI—a review of current knowledge. Journal of Cancer Therapeutics & Research, 2012,1(1):34.

[26] Saracco A, Szabó BK, Tánczos E, et al. Contrast-enhanced ultrasound (CEUS) in assessing early response among patients with invasive breast cancer undergoing neoadjuvant chemotherapy. Acta Radiol, 2016,58(4):394-402.

[27] Lee SC, Grant E, Sheth P, et al. Accuracy of Contrast-enhanced ultrasound compared with magnetic resonance imaging in assessing the tumor response after neoadjuvant chemotherapy for breast cancer. J Ultrasound Med, 2017,36(5):901-911.

[28] Nam K, Eisenbrey JR, Stanczak M, et al. Monitoring neoadjuvant chemotherapy for breast cancer by using three-dimensional subharmonic aided pressure estimation and imaging with US contrast agents: Preliminary experience. Radiology, 2017,285(1):53-62.

[29] Yamamoto S, Suga K, Maeda K, et al. Breast sentinel lymph node navigation with three-dimensional computed tomography-lymphography: A 12-year study. Breast Cancer, 2016,23(3): 456-462.

[30] Rautiainen S, Sudah M, Joukainen S, et al. Contrast-enhanced ultrasound-guided axillary lymph node core biopsy: Diagnostic accuracy in preoperative staging of invasive breast cancer. Eur J Radiol, 2015,84(11):2130-2136.

[31] Matsuzawa F, Omoto K, Einama T, et al. Accurate evaluation of axillary sentinel lymph node metastasis using contrast-enhanced ultrasonography with Sonazoid in breast cancer: A preliminary clinical trial. Springerplus, 2015,4(1):509.

[32] Zhang YX, Wang XM, Kang S, et al. Contrast-enhanced ultrasonography in qualitative diagnosis of sentinel lymph node metastasis in breast cancer: A meta-analysis. J Cancer Res Ther, 2015,11(4):697-703.

[33] Ecanow JS, Abe H, Newstead GM, et al. Axillary staging of breast cancer: What the radiologist should know. Radiographics, 2013,33(6):1589-1612.

[34] Shimazu K, Ito T, Uji K, et al. Identification of sentinel lymph nodes by contrast-enhanced ultrasonography with Sonazoid in patients with breast cancer: A feasibility study in three hospitals. Cancer Med, 2017,6(8):1915-1922.

[35] Sever AR, Mills P, Weeks J, et al. Preoperative needle biopsy of sentinel lymph nodes using intradermal microbubbles and contrast-enhanced ultrasound in patients with breast cancer. AJR Am J Roentgenol, 2012,199(2):465-470.

[36] Cox K, Weeks J, Mills P, et al. Contrast-enhanced ultrasound biopsy of sentinel lymph nodes in patients with breast cancer: Implications for axillary metastases and conservation. Ann Surg Oncol, 2016,23(1):58-64.