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人工智能联合多参数磁共振成像在乳腺非肿块强化病灶中的应用与进展

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摘要:乳腺非肿块型强化(NME)病灶在影像学上缺乏清晰的边界,且不存在明显的占位效应,这一特性使得在超声、乳腺X线及MRI等影像学检查中难以界定。同时,NME病灶型乳腺癌的影像表现与某些乳腺良性病变存在重叠,导致定性诊断标准存在争议。本综述重点从多参数MRI、多模态影像技术以及人工智能应用3个方面阐述当前研究现状,分析现有研究对于提升NME病灶的定性诊断并减少不必要穿刺活检的价值,旨在为乳腺NME病灶未来可能的研究方向提供思路。
关键词:非肿块强化灶;磁共振成像;人工智能;影像组学;多模态

Application and research progress of artificial intelligence combined with multiparameter MRI in breast non-mass enhancement lesions

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Abstract: Non-mass enhancement (NME) lesions of the breast lack clear boundaries and demonstrate no obvious mass effect on imaging, making them difficult to characterize using ultrasound, mammography, and MRI. Furthermore, the imaging features of NME-type breast cancers often overlap with those of certain benign breast lesions, leading to controversy regarding the diagnostic criteria for qualitative assessment. This review focuses on three aspects of the current research landscape: multiparametric MRI, multimodal imaging techniques, and artificial intelligence applications. It analyzes the value of existing studies in improving the qualitative diagnosis of NME lesions and reducing unnecessary biopsies. The aim is to provide insights for future research directions on breast NME lesions.
Keywords: non-mass enhancement lesions; magnetic resonance imaging; artificial intelligence; radiomics; multimodal

乳腺非肿块型强化(NME)病灶在临床和影像诊断良恶性病灶的定性判断中极具挑战性。一般将NME病灶定义为乳腺MRI上无占位效应的小或大的强化区域[1]。影像中常呈现病灶与正常组织交织的形态,这使得临床难以将良性病灶(如乳腺腺病,尤其是硬化性腺病)与恶性病灶(如原位导管癌、浸润性乳腺癌、粘液癌等)之间精准区分[2]。NME病灶在临床诊断中面临形态特征复杂多样、常规影像检查中良恶性病灶表现相似难以区分以及恶性病灶可仅表现为缓慢、渐进的微弱强化,易被误判为良性病灶的挑战。有研究发现NME乳腺癌包含相当比例的原位癌,该研究表明现有单一影像评估方法曲线下面积(AUC)为0.74,其假阳性率为46.3%,提示可能导致不必要的活检[3]。同时,多种检查方式并行或侵入性诊断方法将增加患者生理与心理的负担[4]。依赖单纯的影像诊断思路已难以对NME病灶进行精准诊断。既往针对乳腺癌淋巴血管浸润的研究发现,融合多区域多模态的MRI模型,其诊断效能优于单一区域模型(AUC=0.77、0.72)[5],这也为乳腺癌NME病灶的研究提供了新的诊疗思路。此外,由于NME病灶具有较高的异质性,临床上也需要建立更为全面、系统且精准的诊断标准[6]。

本文旨在系统地回顾多参数MRI、多模态影像与人工智能(AI)在乳腺NME病灶研究领域内的最新进展,分析其在提升诊断准确性、减少不必要穿刺活检中的潜在价值。针对MRI影像技术的协同应用、生物标志物精准补充以及AI技术突破对NME病灶诊断进行讨论,分析当前研究的局限性以及未来研究的方向。

1 多参数MRI成像在乳腺NME病灶中的应用

动态对比增强MRI(DCE-MRI)是一种重要的影像学技术基础,通过监测对比剂在组织中的动态分布,评估组织的血流灌注情况和血管通透性,为肿瘤的诊断和预后提供重要信息[7]。同时,DCE-MRI能提供多种定量信息益于疾病的诊断。

1.1 DCE-MRI半定量及定量参数分析

半定量分析通常涉及时间-信号强度曲线(TIC)类型、AUC等,这些参数可以提供关于病变增强模式的信息,有助于良恶性病变的鉴别。其中TIC类型能够反映

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组织的血流动力学信息，通过检测对比剂首次通过组织时引起的信号强度随时间的变化而生成[8, 9]。研究证实良性NME病变主要呈现为平台型或流入型，而恶性病变则多与平台型或流出型相关[10]。有学者探究TIC类型与乳腺良恶性病变之间的潜在联系，发现与其他有效特征联合能够提升NME病灶的分类性能[11]。也有研究提出基于体素TIC谱的模型在乳腺非肿块恶性肿瘤鉴别方面明显优于三型TIC类型和半定量参数[12]。该方法提供了一种不同于传统参数的分析方法进而捕捉了更深层肿瘤生物学行为的相关信息，因此有助于提升对NME的鉴别诊断能力。

常见的定量参数包括容积转运常数(K^{trans})、速率常数(K_{ep})和血管外细胞外容积分数(V_e)等。这些参数有助于区分良恶性肿瘤，因为恶性肿瘤通常具有更高的血管生成和血管通透性。有研究探讨了药代动力学模型在乳腺癌诊断中的价值(敏感度为86%，特异度为21%)[13]；一项前瞻性研究通过结合超快速DCE-MRI半定量参数(最大斜率、达峰时间、强化时间等)与定量参数(K^{trans}、K_{ep}、V_e)，在鉴别良恶性病变中取得了更加优异的诊断价值(敏感度为85%，特异度为76%)[14]。两项研究均中为混合人群，仅作方法学参照的证据。尽管上述研究未包含NME病灶，但所采用的定量参数研究方法，为NME的研究提供了可借鉴的技术路径。

针对NME病灶的诊断存在特殊性，缺乏明确占位效应而增加了诊断难度[15]。分析定量参数时，结合NME病灶在DCE-MRI表现出的形态学特征在诊断中也发挥了关键作用。在分布类型方面，已有研究证实NME多以局灶性出现，其次是节段样、线样、区域性和弥散分布；内部强化特征最常见的为不均匀强化，其次为均匀强化、集簇状强化和簇环状强化[16]。

1.2 弥散加权成像

弥散加权成像通过检测水分子布朗运动受限程度来反映组织微观结构特征[17]。该技术通过表观扩散系数(ADC)定量评估组织内水分子扩散能力，乳腺癌因其细胞密度较高，通常表现出比良性病变更低的ADC测量值[18, 19]。多项研究支持ADC在初步鉴别乳腺良恶性病灶方面具有良好效能，尤其在区分恶性与良性病变时表现稳定[20, 21]；在鉴别导管原位癌与浸润性癌时，结合弥散加权成像的诊断价值也高于单一TIC类型分析[22]。然而，在需要对不同恶性亚型进一步详细区分[23]或作为独立诊断依据[24]时，其可靠性仍需深入研究。鉴于NME病灶中恶性亚型以导管原位癌为主，其生物学特征上与肿块型乳腺癌存在差异，因此不能直接套用后者ADC截断值标准且目前只有少量小样本单中心研究。针对NME病灶设定特异性的ADC诊断阈值仍需进一步深入研究[20]。不同乳腺MRI参数对比(表1)。

表1 乳腺NME病灶MRI多参数对比

Tab.1 MRI multi-parameter comparison of breast NME lesions

Parameter	Principle	Main clinical application	Characteristics
TIC curve	Dynamic signal change rate of contrast agent	Preliminary screening of benign and malignant lesions	Intuitive display of hemodynamic process
AUC	Area under the time-signal intensity curve	Assessing the overall enhancement degree of the lesion	Correlated with tumor burden
K^{trans}	Transfer rate of contrast agent from blood vessels to interstitial space	Assessing angiogenesis and permeability	Correlated with pathological microvascular density
K_{ep}	Rate constant of contrast agent from interstitial space back to blood vessels	Assisting differentiation between highly aggressive and less aggressive tumors	Indirectly reflects interstitial pressure and lymphatic drainage status
V_e	Extravascular extracellular volume fraction	Quantifying interstitial fibrosis or edema	Associated with radiotherapy sensitivity
ADC	Degree of restricted water molecule diffusion	Differentiating benign from malignant lesions	No need for contrast agent; reflects cellular density

NME: Non-mass enhancement; TIC: Time intensity curve; AUC: Area under the curve; K^{trans}: Volume transfer constant; K_{ep}: Rate constant; V_e: Extravascular extracellular volume fraction; ADC: Apparent diffusion coefficient.

多参数MRI能将多种序列信息叠加并结合影像诊断结果，对病灶类型进行定量分析，为优化乳腺NME病灶的诊断准确性提供一定支持。然而，仅依靠单一模态诊断特异性较高的NME病变仍可能存在与肿块型病变相比假阳性率更高的情况[25]。因此，仍需要多模态MRI协同优化诊断性能。

2 多模态影像技术在乳腺NME病灶中的应用

多模态影像技术通过综合运用乳腺X线摄影、超声和MRI成像等技术手段，为NME病灶的协同诊断提供了更全面的信息。NME在乳腺X线摄影检查中的常见影像学表现包括：微钙化灶、局灶性密度不对称、乳腺组织结构扭曲变形，以及广泛性腺体密度增高等特征性改变[26]。然而，乳腺X线摄影的准确性易受腺体密度影响，导致其对部分NME病变的检出效率、敏感度及特异度存在一定局限性[27]。数字乳腺断层融合技术虽初步显示出诊断潜力，有研究主要针对NME在该研究队列中，数字乳腺断层融合对NME良恶性诊断的符合率

(74.36%)略优于超声(73.72%),但其循证医学证据级别尚待提升[28]。相比之下,MRI技术凭借高分辨率和丰富的功能成像,被视为核心评估手段[29, 30];而超声造影则能提供独特的微血管灌注信息。当前研究的焦点已从单一技术的优化转向多模态信息的融合。如研究尝试构建融合MRI血流动力学参数与超声特征的诊断模型,主要针对包含肿块型或混合病灶的乳腺病变,其研究对象并非仅为NME,在该混合队列中训练集与外部验证集中的诊断效能(AUC分别为0.90、0.89)均优于单一检查方法[31-33];也有研究证实多模态模型的准确性优于多参数模型。这种综合方法表明利用不同模态的影像信息不仅能够揭示更多NME病变细节的价值还存在一定互补性[34]。

有研究进一步按病灶尺寸进行了亚组分析,发现MRI与超声对NME病灶的诊断特异度在<10 mm、10~20 mm及>20 mm三个亚组中呈递减趋势(分别为70%、52%与46.4%),而敏感度在不同尺寸组间均维持稳定(均为100%)[35]。研究发现随着病灶增大,其内部更容易出现坏死、囊变及出血等不同成分的混合。同时正常组织与病灶交织,致使影像学特征复杂化,可能是特异度下降的重要原因[36]。尽管多模态影像技术整合了多种信息,上述因素仍限制了其诊断特异性在较大病灶中的表现。对于上述研究目前尚未有专门针对NME大病灶的多中心验证,因此NME病灶多模态诊断中对于提升对大病灶的鉴别能力仍需深入研究。在此基础上,生物标志物的应用能够提供精准的补充诊断信息,从而提升整体诊断效能。

3 生物标志物在乳腺NME病灶中的应用

在生物学特性方面,生物标志物与NME的临床及影像学表现存在一定关联,可能提示内分泌治疗耐药性、靶向治疗敏感性和高增殖活性等特性。研究发现原位导管癌在MRI上大多表现为节段性或团块状分布,病理分析发现激素受体阴性、人表皮生长因子受体2(HER-2)阳性及Ki-67(Ki-67≥20%)高表达与更高的侵袭性有关[37]。

雌激素受体与孕激素受体是乳腺癌中常见的两种标志物。研究证实,雌激素受体和孕激素受体染色比例越高,肿瘤表现出的更低组织分级与更优无病生存期。而乳腺癌可能表现为HER-2过表达或Ki-67增殖指数升高[38]。非肿块与肿块型病变在分子亚型构成上有所不同,多中心研究发现HER-2过表达型表现为NME的可能性约为其他亚型乳腺癌的20倍[39, 40],但目前该结论尚缺乏专门针对NME人群的大规模分子亚型分布研究进行验证。

对于组织结构相对松散、异质性较高的NME病灶,穿刺活检样本在反映肿瘤整体生物学特征方面存在一定局限。研究显示病灶大小与分布及淋巴结状态与Ki-67表达相关,影像学特征在一定程度上可以辅助预测Ki-67的表达,并为评估NME病灶的预后与疗效提供参考[41]。此外,NME中弥散分布的增强特征也被认为可能与肿瘤增殖活性有关[42]。

对MRI的图像特征进行分析可知,当NME呈节段性分布[43]、背景实质增强[44]伴随低水平时,其恶性风险相对较高。这与第5版乳腺影像学报告和数据系统中提出的簇状环状强化和节段性分布提示恶性较高的预测结论[45]一致。临床实践中,除了使用以上常规生物标志物外还存在BRCA1/2胚系突变用于所有HER-2阴性患者,尤其三阴性乳腺癌患者进行检测[46];PD-L1用于特定阳性晚期三阴性乳腺癌筛查[47]。这些生物标志物为NME的临床诊断与分型提供了重要参考。近年来,影像组学技术在预测生物标志物状态方面展现出潜力,已有研究用该技术分析生物标志物与乳腺癌瘤内瘤周模型的关联性[48]。虽然上述研究是以乳腺癌为主要研究对象,但可以为NME病灶与生物标志物的研究提供一定的方法学参考。当前研究在样本代表性和结果可靠性方面存在局限,未来需要通过更大规模、更系统性的研究来全面阐明NME病灶的特异性生物学标志物特征。

4 AI在乳腺NME病灶中的应用

近年来为克服单一影像学形态分析难以精准诊断的局限性,研究已逐步向影像学功能成像与AI技术相融合发展。当前,机器学习仍是医学AI应用的重要基础,其技术能够整合多维度临床诊断信息,以构建更完善的辅助诊断体系。根据针对癌症和AI的联合研究,目前的研究方向主要涵盖两大方面:基于人工特征提取的传统影像组学方法,以及依托神经网络架构的深度学习技术[49]。影像组学通过从单幅影像衍生出多幅影像并提取和挖掘大量特征,定量分析隐含在医学图像背后的生物学信息[50]。深度学习则通过神经网络自动提取更深层的影像特征,减少人为干预[5]。AI与多参数MRI结合能综合挖掘多种影像信息,量化分析病灶的形态学、血流动力学等参数,可以协助医生更加细致的评估肿瘤的异质性,以达到提升诊断效能的目的。同时通过加入临床特征及肿瘤微环境分析,建立相应预测模型,也能为鉴别诊断提供参考价值。一项专门针对NME病灶的乳腺影像学报告和数据系统判定及鉴别诊断研究中,研究者基于150例样本,对影像组学与深度学习的性能进行了比较;在训练集和中,单纯影像诊断准确性为64%;支持向量机模型准确率为80.4%(AUC=0.88);而ResNet50深度学习模型的准确率则达到91.5%

(AUC=0.97)[51]。该研究数据结果显示传统影像组学与深度学习都能取得较好的预测性能,二者相较之下深度学习在NME病灶的表现更好。值得关注的是,目前多数模型缺乏独立外部验证,所得结果会在普适性和可靠性方面存在一定的局限性。通过对乳腺癌或其他癌症的研究中,也可以得到关于NME病灶的相关启示。影像组学特征反映了病灶的异质性、强化方式、强化程度等信息[52]。这些特征可以用于肿瘤诊断、预后与生存分析等,对NME的恶性风险进行预测,为临床处理乳腺NME提供决策依据[52]。而深度学习则挖掘处理高维复杂数据,探究人眼无法识别的生物学关联[53]。也有研究尝试将临床、影像特征与机器学习结合预测淋巴结状态,通过约登指数将模型评分>65.4定义为预测存在淋巴结转移,在此条件下假阳性率低至3.7%,提示其潜在的临床应用价值[54],但该性能指标仍需在更广泛的人群中进行外部验证。在实际应用中根据不同临床需求,选用传统影像组学、深度学习或多模态融合的方式进行协助诊断。可见基于机器学习的多模态融合并非独立使用,而是贯穿传统影像组学与深度学习的共同环节。乳腺NME病灶影像组学与机器学习模型诊断性能(表2)以样本量的大小、外部验证的有无和研究类型这三个方面为标准,对其研究进行证据等级判定。

表2 乳腺NME病灶影像组学与机器学习模型诊断性能

Tab.2 Diagnostic performance of radiomics and machine learning models for breast NME lesions

Study	Sample size	NME-disease	External validation	Results	Research type	Evidence level
Kayadibi[3]	178	Yes	Yes	Clinical+imaging AUC=0.942	Retrospective	Medium
Li[13]	28	No	No	DCE+pharmacokinetic AUC=0.93	Retrospective	Low
Niu[31]	183	Yes	Yes	US+MRI AUC=0.901	Prospective	High
Zhou[51]	150	Yes	No	ResNet50 AUC=0.97	Retrospective	Medium
Zhang[54]	775	No	Yes	Clinical+imaging AUC=0.906	Retrospective	Medium

NME: Non-mass enhancement; AUC: Area under the curve; DCE: Dynamic contrast enhanced; US: Ultrasound; MRI: Magnetic resonance imaging. The core results are all the best performance indicators obtained by each study on its training set. The criteria for evidence level assessment are as follows: High-it is required to simultaneously meet the conditions of a large sample size (n>150), have external validation, and be a prospective study design; Medium-it meets the condition of a large sample size but lacks external validation, or has a limited sample size but has external validation; Low-it is a retrospective study with a small sample size (n<50) and no external validation. Some are non: NME lesions and are only used as methodological references.

在乳腺NME病变的鉴别诊断中,影像组学特征的提取和分析有助于支持诊断的准确性[55]。有研究发现深度学习依赖的自动勾画优于传统组学模型的预测结果[56],有学者同样利用深度学习与自动勾画技术证明了优化勾画方式能够有效提升模型性能[57]。结合临床病理特征与影像特征的系统研究取得了较好的预测性能,且在保持较高敏感度的同时,能够降低活检率[58, 59]。然而,现有AI模型在实际临床应用时仍需克服多重挑战。NME病灶患者占比相对较低,因此纳入研究患者可能会存在一定偏倚;深度学习模型的“黑箱”特性导致可解释性不足;不同影像设备之间扫描协议的差异难以使得模型进行推广。在乳腺癌影像研究领域中,基于机器学习的研究已从传统的肿瘤内异质性分析,逐步拓展至对肿瘤周围微环境的多区域分析,研究发现肿瘤周围微环境能够表征抗肿瘤免疫应答和侵袭转移等信息[60, 61]。这也为学者利用机器学习针对NME病灶肿瘤周围区域的研究提供了参考方向。

5 小结与展望

影像技术的持续发展为乳腺NME病变的诊断和治疗提供了新的机遇与挑战。通过融合多参数、多模态影像信息与AI辅助诊断,已成为对病灶进行全面评估的参考依据。然而,在临床实践中仍存在一些局限性,如NME病灶相对较少且边界模糊,导致高质量、大规模数据集的构建与病灶精准分割存在困难;现有模型的泛化能力与临床可信度,高度依赖于多中心外部验证以及对模型决策逻辑的可解释性分析。因此未来研究预计将聚焦于以下几个方面:首先,整合机器学习技术,开发具有自适应能力的诊断模型,降低人为处理图像的主观局限性,该技术实现有赖于高质量标注数据与稳健算法框架的支持;其次,推动多中心NME患者数据库建设,实现该数据库需采用标准化数据采集规范进而缓解样本异质性问题,增强数据的泛化能力;最后,推动影像与基因、病理等信息的跨模态整合,需建立跨学科协作机制与标准化的数据整合流程,从而将影像特征真正转化为可指导治疗决策的预后指标。提高乳腺NME病灶的诊断准确性和治疗有效性,为实现乳腺癌早期无创精准诊断提供核心技术支撑。

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