

# 影像组学在乳腺癌分子生物学指标及其分子分型预测中的研究

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**摘要:**乳腺癌是女性中最常见的恶性肿瘤,其发病率和死亡率均居女性癌症首位。早期精准诊疗对改善患者预后具有决定性意义。基于免疫组织化学检测的分子分型体系已成为临床治疗策略制定的关键,但传统病理活检因其侵入性特征存在应用局限性。影像组学作为新兴的影像研究方法,在预测分子生物学指标及分子分型具有巨大的潜在应用前景。本文基于不同影像检查的影像组学在乳腺癌分子生物学指标及分子分型的研究进展进行综述。

**关键词:**影像组学; 乳腺肿瘤; 分子分型; 分子生物学指标

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## Research on radiomics in the prediction of molecular biological indicators and molecular subtypes of breast cancer

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**Abstract:**Breast cancer is one of the most common malignant tumors in women. It has the highest incidence and mortality among the cancers in women. Early precise diagnosis and treatment play a decisive role in improving patient prognosis. The molecular classification system based on immunohistochemical detection has now become a key factor in formulating clinical treatment strategies. However, traditional pathological biopsy has limitations in application due to its invasive characteristics. As an emerging field within imaging research, radiomics presents immense potential for predicting molecular biological indicators and molecular subtyping. This article reviews research progress on radiomics based on different imaging modalities for breast cancer molecular biomarkers and molecular subtyping.

**Key words:** Radiomics; Breast tumor; Molecular subtyping; Molecular biological indicators

乳腺癌(Breast cancer, BC)是女性最常见的癌症,根据2022年全球癌症数据报道,该病新发病例为230万例(占有所有癌症的11.6%),死亡病例达66.5万例(占有所有癌症死亡的6.9%)<sup>[1]</sup>。早发现和早治疗是改善BC预后的关键<sup>[2]</sup>。在BC治疗和管理中,分子亚型的确定决定着治疗方案选择和预后评估。分子亚型一般通过有创病理学检查获得。近年来,影像组学作为一种高通量提取特征的无创性技术在肿瘤鉴别诊断、病理预测及预后评估等方面进行了广泛研究<sup>[3-4]</sup>。本文基于乳腺影像组学在预测BC分子生物学指标及其分子分型的研究进行综述。

### 1 乳腺癌分子生物学指标与其分型

根据最新的欧洲肿瘤医学学会早期BC管理指南,新辅助全身治疗方案的选择主要基于活检的分子亚型<sup>[5]</sup>。BC的异质性特征体现在癌细胞的基因组、表观基因组、转录组和蛋白质组谱的变化<sup>[6]</sup>。基因表达谱分析被认为是BC分类的最佳方法,评估分子生物学指标如雌激素受体(Estrogen receptor, ER)、孕激素受体(Progesterone receptor, PR)、表皮生长因子(Human epidermal growth factor receptor 2, HER-2)和增殖指数Ki-67是至关重要的<sup>[7]</sup>,因为其

不仅是BC预后的重要决定因素,还决定着BC亚型<sup>[8]</sup>。乳腺癌的分子亚型根据St. Gallen Consensus Conference 2013<sup>[9]</sup>定义,后又将BC拓展为5种分子亚型:Luminal A型、Luminal B HER-2阴性型、Luminal B HER-2阳性型、HER-2富集型和三阴性型<sup>[10]</sup>。最近,HER-2低表达BC的命名法被提出<sup>[11]</sup>,与HER-2阴性和HER-2阳性BC相比,HER-2低表达BC具有独特的临床和突变特征。因此,根据HER-2表达情况将乳腺癌分为HER-2阳性、HER-2低表达、HER-2-zero 3个亚型,可以更清晰地指导浸润性导管癌患者的预后和管理。随着对BC分子亚型更深入的理解,未来有望开发出更多针对性的治疗方法,从而进一步提高患者的生存率和生活质量。

## 2 影像组学在预测乳腺癌分子生物学指标及其分型中的运用

**2.1 影像组学的概述** 影像组学是一种高通量技术,它通过从医学成像数据中提取和分析大量的定量特征,为临床诊断和研究提供了新视角。这些特征采用计算机算法从医学图像中提取数字化特征,并将其转换为高维数据集,进而解析病变组织的异质性,提供传统影像上肉眼无法分辨的隐藏信息<sup>[12]</sup>。影像组学的应用范围广泛,包括诊断、预后评估、预测等,研究者利用机器学习技术探索这些定量数据与生物学或临床结果之间的潜在联系,其流程包括:图像采集—感兴趣区分割—特征提取和选择—模型建立和验证<sup>[13]</sup>。影像组学特征提供关于灰度模式、像素间关系以及影像学图像的形状和光谱特性的信息,同时提取的特征可以开发出模型,并为个性化诊断和治疗提供指导依据<sup>[14]</sup>。

**2.2 基于X线检查** 乳腺X线检查是BC诊断的主要方式之一,是进行BC筛查的最佳检查方法,具有禁忌证少、检查费用低、速度快、图像易获得等优点。因此,通过常规乳腺X线检查预测分子亚型将具有重要的临床价值。

**2.2.1 全视野数字乳腺X线摄影(Full-field digital mammography, FFDM)** FFDM广泛应用于BC筛查的成像技术,在检测微钙化方面具有显著优势<sup>[15-16]</sup>。近年来研究通过影像组学技术探索X线图像与分子生物学指标的相关性,其中三阴性乳腺癌(Triple-negative breast cancer, TNBC)的预测效能尤为突出。Ma W等<sup>[17]</sup>用数字乳腺X线摄影中

提取的39个定量影像组学特征,并使用最小绝对收缩年龄和选择算子(Least absolute shrinkage and selection operator, LASSO)方法选择预测特征在预测TNBC这种分子亚型的受试者工作特征(Receiver operating characteristic, ROC)曲线的曲线下面积(Area under the curve, AUC)达到0.865。另一项研究通过提取396个影像组学特征构建TNBC预测模型, AUC达0.84<sup>[18]</sup>。这些研究表明,基于FFDM图像的影像组学预测TNBC效果较好。

**2.2.2 数字乳腺断层摄影(Digital breast tomosynthesis, DBT)** 尽管FFDM已广泛应用于BC筛查,但存在明显的图像重叠,尤其对于致密型乳腺的BC检出率较低。作为FFDM的补充,DBT展现出了更低的召回率和更高的癌症检出率,正日益成为BC筛查和诊断的重要工具<sup>[19]</sup>。DBT影像组学在分子分型预测中具有独特价值。Tagliafico A S等<sup>[20]</sup>纳入了40例患者并利用影像组学方法比较DBT在致密型和非致密型乳腺组织中的BC检测能力,发现影像组学特征在癌变和正常乳腺组织中存在差异,其中能量、熵、异质性3个影像组学特征证实与肿瘤大小和PR状态相关。Son J等<sup>[21]</sup>进一步通过DBT合成的乳腺X线摄影(Synthesized mammography, SM)提取影像特征并构建预测模型,对不同亚型的BC进行预测,其中头尾位联合内外斜位的模型在预测TNBC、HER-2和Luminal亚型时AUC分别达到0.838、0.556和0.645,结果证明了X线在预测TNBC上更具优势,且联合瘤内-瘤周特征可进一步提升预测性能。Niu S等<sup>[22]</sup>结合DBT与DM的多区域特征使Luminal A/B亚型验证集AUC分别达0.773和0.807。另有研究<sup>[23]</sup>通过瘤周特征实现HER-2表达的高效预测(验证集AUC=0.850),凸显DBT多维度影像组学的临床应用潜力。

**2.2.3 对比增强乳腺X线摄影(Contrast enhanced mammography, CEM)/对比增强能谱乳腺X线摄影(Contrast enhanced energy spectrum mammography, CESM)** CESM是在FFDM基础上用碘化造影剂显示血管及双能量采集减影,来明确恶性肿瘤的位置,从而提高预测的准确性、降低假阳性结果和良性病变活检的发生率,特别是在致密型乳腺病例中有着更高的诊断价值<sup>[24-25]</sup>。La Forgia D等<sup>[26]</sup>用低能量(Low energy, LE)和重组(Reconstructed, RC)CESM的DICOM中逐层勾画

感兴趣区域(Region of interest, ROI),分别从中提取7个影像组学特征,预测ER、PR、HER-2、Ki-67、TNBC的AUC分别为0.827、0.821、0.834、0.798、0.908,提示CESM在预测TNBC上优于其他指标。联合头尾位与斜位视角可进一步提高TNBC预测灵敏度<sup>[27]</sup>。Nicosia L等<sup>[28]</sup>拓展CESM的影像组学特征与乳腺肿瘤特定受体模式之间的关系。通过单变量Logistic回归研究特征与各评估终点(ER、PR、Ki-67、HER-2阳性、TNBC)的关系,在ER与PR的预测上有着相同的组学特征,或与临床治疗靶点关联机制相关。以上研究表明,CESM影像组学在乳腺癌早期诊断、分子分型及个体化治疗策略制定中具有重要应用价值。

**2.3 基于超声(Ultrasound, US)检查** 乳腺超声(Breast ultrasound, BUS)成像以其无辐射、安全、低成本、成像速度快、可重复等特点,已被公认为乳腺肿块检测和诊断必不可少的影像学工具<sup>[29-30]</sup>。

**2.3.1 基于乳腺超声** BUS是一种多角度扫描病变的技术,通常选取病变处最大的超声切片进行分析。既往研究均用术前超声影像学特征来预测BC的分子亚型、HER-2表达、Ki-67表达<sup>[31-36]</sup>。Wu J等<sup>[37]</sup>基于常规超声提取瘤内组学特征构建影像组学评分(Radscore),联合临床特征建立的列线图模型对分子分型的预测效能显著优于单一临床模型,且Radscore独立预测能力与列线图比较差异无统计学意义( $P>0.05$ ),表明其具有较高的预测效能。进一步研究发现,整合瘤周超声组学特征可使Ki-67表达预测模型验证集AUC提高,其中在瘤周10 mm的影像组学特征联合后AUC最高,为0.78<sup>[38]</sup>。值得注意的是,联合肿瘤大小等形态学参数可优化激素受体(Hormone receptor, HR)预测效能,Wu J等<sup>[39]</sup>将灰度超声的长轴及短轴的影像特征构建的Radscore以及单因素(肿瘤大小)独立预测因子联合构建模型预测HR表达,HR验证集AUC达0.822,凸显形态-功能特征融合的临床意义。上述证据表明,超声影像组学联合多维特征可为乳腺癌分子分型无创评估提供新途径。

**2.3.2 基于对比增强超声造影(Contrast-enhanced ultrasound images, CEUS)** CEUS在BC的诊断中能提供肿瘤的动态血流灌注信息以及更容易发现坏死区,显著提高诊断准确性,CEUS影像组学特征与分子分型密切相关。Bene I等<sup>[40]</sup>在CEUS下提取

的影像组学特征预测BC分子生物学指标,发现在预测HER-2、ER、PR上分别有1个、1个、2个强相关性的影像组学特征,并在预测性能上特异性均超过80%,证实CEUS对分子标志物表达的高特异性预测能力。进一步研究显示,联合US与CEUS构建多模态模型可显著提升分子标志物预测精度<sup>[41]</sup>。上述研究表明,CEUS的影像组学特征在BC分子分型中的诊断价值,为个性化治疗提供了科学依据。随着技术的不断发展,预计未来CEUS将在BC的诊断和治疗中发挥更大作用。

**2.4 基于磁共振成像(Magnetic resonance imaging, MRI)检查** MRI具有软组织对比度高、多参数成像能力、无侵入性、高分辨率成像、三维成像、功能成像等优势,尤其是在数据挖掘上,在影像组学领域运用广泛。

**2.4.1 平扫磁共振成像** 弥散加权成像(Diffusion weighted imaging, DWI)通过量化肿瘤水分子扩散受限程度,为乳腺癌分子分型预测提供功能影像依据。研究显示,基于高b值DWI与ADC图像融合分割病灶,预测分子分型的准确率超过0.9<sup>[42]</sup>。Ni M等<sup>[43]</sup>进一步整合T1-DCE、T2WI及ADC多模态MRI特征,在构建模型前,用6种机器学习分类器来提高鲁棒性,接着采用多变量Logistic回归分析和基于明池信息准则的反向逐步回归分析,建立Nomogram。结果发现,随机森林(Random forest, RF)联合ADC-map特征在验证集AUC达0.826,而融合临床特征后AUC提升至0.868,证实多维度数据协同可优化预测性能。另一项研究利用相同的方法将MRI测得的肿瘤最大径及ADC值做Nomogram,直观展现对HER-2的预测能力<sup>[44]</sup>。

在瘤周特征方面,Li C等<sup>[45]</sup>基于多区域DWI和ADC特征的Radscore,并结合临床因素评估BC的HER-2表达。结果显示,AUC在训练集及验证集分别为0.860、0.790,较单一区域特征显著提升,提示瘤周微环境对分子异质性的潜在影响。值得注意的是,肿瘤解剖位置与瘤周水肿模式存在关联。如肿瘤位于外上象限时以瘤周水肿多见,肿瘤位于内象限时以胸前水肿多见,肿瘤位于内下象限时以皮下水肿为主,中心肿瘤以弥漫性水肿多见,基于水肿特征的模型对PR及Ki-67表达预测AUC分别为0.659、0.621<sup>[46]</sup>,虽效能有限,但为探索肿瘤-宿主交互作用提供了新视角。上述研究凸显DWI影像

组学在乳腺癌无创分子分型评估中的临床应用潜力。

#### 2.4.2 动态增强磁共振成像 (Dynamically enhanced magnetic resonance imaging, DCE-MRI)

DCE-MRI通过无创评估肿瘤血流动力学特征,为乳腺癌分子分型预测提供重要依据,不同增强时相的影像组学特征具有差异化价值。Leithner D等<sup>[47]</sup>采用DCE-MRI首期图像提取的影像组学特征评估BC受体状态和分子亚型方面的诊断性能,结果显示,基于影像组学特征构建的分类模型在训练集中预测准确度均高于0.8,其中,Luminal B亚型与其他亚型的区分性能尤为突出,可能与其在影像组学上表现出更具特异性的纹理或几何特征有关。进一步进行外部验证,发现Luminal A与Luminal B、Luminal B与三阴性乳腺癌的验证准确度分别为0.794、0.771,表明所构建的影像组学模型具有一定的泛化能力。Huang T等<sup>[48]</sup>基于DCE-MRI第二期图像提取影像组学特征,用于术前鉴别Luminal型与非Luminal型BC,其模型在训练集和测试集中的AUC值分别为0.86和0.80,说明该期像提取的影像组学特征同样具有较好的鉴别能力。然而Huang G等<sup>[49]</sup>对比了早期、峰值期及延迟期影像特征,发现延迟期提取的特征数量最多,在预测性能上,延迟期与联合早期、峰值期的能力相似,这表明不同期像均有价值,但在延迟期上似乎更具价值。值得注意的是,联合多模态参数可显著提升预测效能,Feng S等<sup>[50]</sup>基于DCE-MRI第四期图像和ADC的全肿瘤区域影像组学模型预测BC患者的Ki-67状态,在训练集及验证集的AUC分别为0.839、0.795。另有研究<sup>[51]</sup>基于DWI联合DCE-MRI第三期图像提取影像组学特征,构建术前预测乳腺癌HER-2表达状态的联合模型。该模型在训练集中的AUC值达到0.843,表明多序列MRI影像组学特征协同分析能够显著提升预测性能,体现了多参数影像联合在乳腺癌分子标志物评估中的重要价值。

瘤周影像组学对分子异质性的解析作用日益受到关注。Braman N等<sup>[52]</sup>通过多中心研究证实,联合瘤内-瘤周特征的HER-2预测模型在外部验证集AUC达0.69,较单一区域特征显著优化。Zhong S等<sup>[53]</sup>基于瘤周特征预测ER/PR状态的验证集AUC分别为0.763和0.833,进一步支持其临床应用价值。Li C等<sup>[54]</sup>的研究方法与Braman N等<sup>[52]</sup>相近,其

一并纳入了Ki-67的预测,结果显示,合并瘤内和瘤周的AUC预测HER-2、Ki-67分别为0.713、0.749。为了研究瘤周特征最佳范围,Zhang S等<sup>[55]</sup>纳入瘤内及最佳瘤周的组学特征预测分子分型,最终将瘤周6 mm定义为最佳瘤周区域,而预测HER-2富集型的最佳瘤周范围为8 mm。该研究的外部验证集AUC分别为0.791、0.707、0.852,这避免了模型过拟合,在临床实用性及可靠性上有着较好的说服力。Feng S等<sup>[56]</sup>采取了DCE-MRI不同期像的强化像素强度将整个肿瘤区域划分为3个亚区。该研究使用LR模型来选择与Luminal分类相关的独立因素,包括Radscore、HER-2表达情况和肿瘤组织学分级。最终将临床病理因素与Radscore相结合绘制Nomogram,得出该Nomogram能够无创性地区分Luminal型BC。随着研究深入和技术发展,未来可期待在MRI影像组学领域有望整合更多维度的数据,为BC的分型鉴别提供更多帮助。

#### 2.5 氟-18脱氧葡萄糖正电子发射断层扫描 (Fluorine-18 fluorodeoxyglucose positron emission tomography, <sup>18</sup>F-FDG PET)

<sup>18</sup>F-FDG PET通过量化肿瘤糖代谢活性,为乳腺癌分子异质性评估提供功能影像依据。

Chen Y等<sup>[57]</sup>通过结合PET/CT预测BCHER-2的表达,在Xgboost分类器中效果最好,训练集和验证集的AUC分别为0.76和0.72。Liu J等<sup>[58]</sup>通过多中心数据整合多参数PET/CT特征,证实联合特征可显著提升分类精度。Umutlu L等<sup>[59]</sup>运用乳腺<sup>18</sup>F-FDG PET/MRI同时成像的性能鉴别Luminal A和Luminal B分型的AUC高达0.98,展现卓越的分辨能力。此外,Romeo V等<sup>[60]</sup>联合PET代谢参数与ADC值构建的TNBC预测模型验证集AUC达0.887,进一步拓展了分子亚型预测的维度。这些研究不仅验证了PET影像组学在乳腺癌代谢异质性解析中的临床价值,更为精准治疗决策提供了多维生物标志物支持。

### 3 小结与展望

影像组学在预测BC分子分型中显示出巨大的潜力。通过挖掘X线钼靶、超声、MRI、PET等多种影像学检查的数据,并高效地处理和分析大量的影像数据,在获取病理结果之前预测BC的特定分子亚型,从而减少对侵入性检查的依赖。结合机器

学习和深度学习技术,多模态、多序列、多视角、瘤周联合等方式能够为乳腺癌患者个性化的治疗提供科学依据。然而,影像组学特征选择、特征可解释性以及不同成像设备、参数导致的不可复制性问题仍是挑战。随着不同医疗机构间的协作、影像数据量的增大及相关处理技术进步,影像组学有望在BC基因层面实现更深入的探索,为此类患者的个性化精准医疗提供帮助。

所有作者均声明不存在利益冲突关系。

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