

DOI: 10.16781/j.CN31-2187/R.20240704

· 综述 ·

乳腺癌新辅助化疗后疗效的预测：多种成像方式的比较

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[摘要] 影像学检查在预测乳腺癌新辅助化疗后疗效中起到了重要作用, 且不同的成像方式有各自的优势和价值。本综述对比了乳腺X线摄影、MRI、超声、正电子发射断层扫描在乳腺癌新辅助化疗后疗效方面的预测性能。MRI特别是动态增强MRI及影像组学和人工智能的结合显示出较高的灵敏性和特异性, 逐渐成为了首选检查方式。随着技术的不断进步和研究的深入, 这些成像方式有望在乳腺癌的精准治疗和个体化治疗中发挥更加重要的作用。

[关键词] 乳腺肿瘤; 新辅助化疗; 成像方式; 参数指标; 影像组学; 人工智能

[引用本文] 孙德正, 董文彦, 方敏, 等. 乳腺癌新辅助化疗后疗效的预测: 多种成像方式的比较[J]. 海军军医大学学报, 2025, 46(4): 524-529. DOI: 10.16781/j.CN31-2187/R.20240704.

Prediction of efficacy of neoadjuvant chemotherapy for breast cancer: a comparison of multiple imaging modalities

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[Abstract] Imaging modalities play an important role in predicting the efficacy of neoadjuvant chemotherapy for breast cancer, and different imaging modalities have their own advantages and value. In this review, the performance of mammography, magnetic resonance imaging (MRI), ultrasound, and positron emission tomography in predicting the efficacy of neoadjuvant chemotherapy for breast cancer was compared. Among them, MRI, especially dynamic contrast-enhanced MRI, and the combination of imaging omics and artificial intelligence, has shown high sensitivity and specificity, and has gradually become the preferred examination method. With the continuous progress of technology and research, these imaging modalities are expected to play more important roles in the precise and individualized treatment of breast cancer.

[Key words] breast neoplasms; neoadjuvant chemotherapy; imaging modality; parameter index; radiomics; artificial intelligence

[Citation] SUN D, DONG W, FANG M, et al. Prediction of efficacy of neoadjuvant chemotherapy for breast cancer: a comparison of multiple imaging modalities[J]. Acad J Naval Med Univ, 2025, 46(4): 524-529. DOI: 10.16781/j.CN31-2187/R.20240704.

国际癌症研究机构2022年数据显示, 乳腺癌是女性中最常见和死亡人数最多的癌症^[1]。它的治疗方式主要包括局部治疗和全身治疗^[2]。在传统的辅助治疗中, 全身治疗在手术治疗之后, 而新辅助化疗(neoadjuvant chemotherapy, NAC)则在手术治疗之前, NAC正在成为局部晚期乳腺癌的标准治疗^[2-3]。NAC的疗效可分为病理完全缓解

(pathological complete response, pCR)、病理部分缓解(pathological partial response, pPR)、疾病进展(progressive disease, PD)和疾病稳定无缓解(stable disease with no response, SDNR)4类。评估NAC对肿瘤的疗效在制订个体化治疗方案及指导后续辅助治疗中有重要作用。

多种影像学方式被用于评估乳腺原发肿瘤和

[收稿日期] 2024-10-16 [接受日期] 2024-12-17

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腋窝淋巴结状态。乳腺X线摄影(mammography)、MRI和超声是常见的成像方式,正电子发射断层扫描(positron emission tomography, PET)常用于怀疑或已知的转移性乳腺癌^[4],这些成像方式可以早期预测NAC治疗乳腺癌的疗效。近年来,随着计算机技术的发展,影像组学和人工智能在医学领域的发展日新月异。影像组学可以将医学影像转化为形状特征、纹理特征等可挖掘的数据,用于临床决策支持^[5]。而人工智能也已成为处理复杂影像数据的优秀工具,在肿瘤的诊断、精准治疗和预后改善方面发挥了重要作用^[6]。本综述主要阐述和比较了多种成像方式在预测乳腺癌NAC疗效中的应用。

1 乳腺X线摄影

自20世纪60年代以来,乳腺X线摄影一直用于乳腺癌的筛查和诊疗。Azam等^[7]的回顾性研究表明乳腺X线摄影中钙化与浸润性疾病的相关性较差,还高估了NAC后残留病灶的程度。此外, Kim等^[8]研究也证明NAC后乳腺X线摄影残余微钙化与癌症残留程度无关。随着技术的改进,对比增强能谱乳腺X线摄影(contrast-enhanced spectral mammography, CESH)得到了越来越广泛的应用,其使用静脉注射碘造影剂以类似于MRI的方式来评估患者乳腺新生血管情况。CESH采用双能量成像技术,通过将碘造影剂处理前后获得的低能和高能图像相减获得所需要的减影图像^[9-10]。当前CESH已成为对MRI禁忌患者可行且准确的替代方法,而且在准确性相同的情况下人们更喜欢使用CESH^[11-12]。

多项研究对比了CESH和MRI对乳腺癌NAC疗效的预测性能。在Barra等^[13]的前瞻性研究中, CESH检测残留病灶的灵敏度、特异度、阳性预测值和阴性预测值分别为76%、87.5%、95%和86.4%,而MRI分别为92%、75%、92%和75%;此外, CESH、MRI测量的肿瘤大小与残留组织病理学检测到的肿瘤大小之间的平均差异分别为0.8 cm和1.8 cm。该研究结果表明CESH与MRI在检测残留病灶方面均显示出较高的阳性预测价值和特异性。在Zhang等^[14]的回顾性研究中,通过影像组学方法提取了CESH中肿瘤感兴趣区的13个影像组学特征,并构建了包含影像组学评分

和临床危险因素的列线图模型。该模型在训练数据集中预测pCR的AUC值为0.906,在测试数据集中AUC值为0.790,显示出对乳腺癌NAC后pCR较好的预测性能。

2 MRI

MRI是一种常用于乳腺的无创成像技术,通过分析人体组织中的原子核磁共振现象生成图像,具有出色的软组织分辨率。借助特定的MRI技术, MRI还可以获得肿瘤灌注、血管通透性、代谢状态等功能信息^[15]。随着乳腺成像线圈的开发和改进及磁共振造影剂的应用,动态对比增强磁共振成像(dynamic contrast-enhanced magnetic resonance imaging, DCE-MRI)得到了广泛应用。它不仅成为乳腺癌诊断中最灵敏的工具^[16],也是目前评估NAC疗效最准确的成像方式^[17-19]。在Sudhir等^[20]的前瞻性研究中,对56例患者同时采用乳腺X线摄影、超声检查和MRI评估NAC疗效。结果显示, MRI在预测pCR方面的性能要优于乳腺X线摄影和超声检查, AUC值分别为0.86、0.68和0.65。此外, MRI在预测不同分子亚型乳腺癌NAC疗效方面表现出了巨大差异。在Kuzmova等^[21]对167例患者的回顾性研究中, MRI预测NAC后pCR的总体准确度为77.3%,其中预测三阴性乳腺癌(triple negative breast cancer, TNBC)的准确度最高,为87.5%,这可能与TNBC对造影剂的高摄取有关。

弥散加权成像(diffusion weighted imaging, DWI)是一种通过观察水分子在乳腺组织中的扩散情况来反映乳腺组织信息的技术,是DCE-MRI的重要补充成像技术。其中,表观扩散系数(apparent diffusion coefficient, ADC)是DWI的定量测量指标。在Partridge等^[22]的前瞻性研究中,通过对NAC治疗前、治疗早期、治疗中期和治疗后的ADC差值(Δ ADC)进行分析,发现 Δ ADC在治疗中期(12周)和治疗后表现出较好的预测效果,表明DWI上乳腺肿瘤ADC的变化可用于预测NAC的pCR。

NAC的疗效可以通过MRI的参数及肿瘤大小的变化来评估,但在治疗早期这些指标的变化往往不明显。因此, Sutton等^[23]的回顾性研究中将MRI和影像组学相结合,对比了单纯影像组学模型

与影像组学和分子亚型的组合模型的预测性能,结果显示后者对pCR的预测结果更佳,训练集AUC值为0.80,验证集AUC值为0.78。此外,Zheng等^[24]通过回顾性研究对比了肿瘤内、瘤周区、背景实质增强区及三者的融合模型,发现融合模型表现出更好的pCR预测效果,训练集AUC值为0.891,验证集AUC值为0.861。

除了对MRI感兴趣区的研究,多模态成像相关研究也在不断深入。Liu等^[25]的回顾性研究构建了T2加权成像(T2-weighted imaging, T2WI)、DWI、增强序列及多参数MRI的影像组学模型以预测NAC后的pCR,结果表明多参数MRI的影像组学模型的AUC值为0.79,在4种方法中预测性能最高,并且在激素受体阳性(hormone-receptor positive, HR⁺)乳腺癌、人表皮生长因子受体2阴性(human epidermal growth factor receptor 2 negative, HER2⁻)乳腺癌和TNBC中均表现出良好的预测能力。在一项涉及1262例患者的多中心研究中,分别在NAC开始前和完成后从T2WI、DCE-MRI和DWI图像中勾画肿瘤和瘤周感兴趣区,并通过机器学习和深度学习提取影像组学特征,构建了基于NAC前、NAC后、两者差值(delta)及堆叠数据(整合NAC前、NAC后、delta)在不同分子亚型乳腺癌中的预测模型^[26]。结果表明,与机器学习模型相比,深度学习模型在所有分子亚型乳腺癌中的pCR预测性能更优。与NAC前、NAC后、delta模型相比,堆叠模型在训练集HR⁺/HER2⁻、HER2⁺和TNBC亚型中的AUC值更高,分别为0.959、0.974和0.958,在3个外部验证队列中的AUC值分别为0.882~0.908、0.896~0.929和0.837~0.901。

肿瘤异质性(tumor heterogeneity, TH)是指构成单个肿瘤的细胞表型存在变异性,是癌症的一个显著特征,常表现为细胞形态、增殖、转移、代谢、血管生成等方面的差异^[27-29]。TH常导致乳腺癌患者NAC疗效的差异。亚区域分析作为一种新兴的方法,将医学影像中的肿瘤区域划分为不同包含相似成像特征体素的亚区域,以对TH进行评估^[30-31]。一项涉及1589例乳腺癌患者的多中心回顾性研究采用线性交互聚类方法将肿瘤区域聚类成不同的亚区域,通过在亚区域内提取瘤内生态多样性特征构建肿瘤内异质性(intratumor

heterogeneity, ITH)模型^[32]。结果表明,ITH模型在训练集中预测NAC后pCR的AUC值为0.77,且ITH指数是pCR重要的独立预测因子(OR=5.03, P<0.001),可为患者风险分层提供依据;整合了ITH模型、临床模型和影像组学模型的混合模型在训练集的AUC值为0.90,在外部测试集的AUC值为0.83~0.87,都表现出的良好预测性能。这种基于亚区域分析的方法可能成为量化TH的无创评估方法。

3 超声检查

超声检查是一种动态检查,通过高频机械声波在乳腺组织中的传导和反射而生成图像。正常和患病乳腺组织之间声波的穿透和反射差异能够显示出乳房内部的形态,从而辅助判断乳腺肿块的大小、形态、位置及血流情况等。Fernandes等^[33]纳入92例乳腺癌患者的研究中采用了超声应变弹性成像,发现pCR和非pCR组均表现出肿瘤硬度的显著变化,在NAC后第2周和第4周时肿瘤硬度相较于基线明显下降(均P<0.01),且在第2周时两组的肿瘤应变比相较于基线也下降(均P<0.01)。肿瘤应变比在朴素贝叶斯分类器中术前预测pCR的灵敏度为84%,特异度为85%,AUC值为81%。这项研究结果表明肿瘤硬度变化可以作为NAC早期肿瘤反应标志物。此外,Yuan等^[34]纳入98例患者进行回顾性研究,采用了剪切波超声弹性成像,发现其最大弹性与实体瘤疗效评价标准指数相关。Yu等^[35]的回顾性研究构建了深度学习影像组学模型,该模型整合了NAC前超声组学特征和临床特征,在训练集和验证集均取得了良好的NAC疗效预测性能,AUC值分别为0.962和0.939。

4 PET

PET是一种常用的评价肿瘤糖酵解代谢的核素成像方法。PET通过应用放射性核素标记参与人体代谢的生理物质并在体外用显像仪器显示,其能够精准地反映肿瘤组织与正常组织细胞代谢的差异。该方法在乳腺癌分期、复发评估和疗效预测方面应用广泛。

标准化摄取值(standard uptake value, SUV)是评价PET葡萄糖摄取程度的指标,不同的组织学类型SUV不同。在Lee等^[36]纳入87例晚

期乳腺癌患者的回顾性研究中,定义了3个周期化疗后最大SUV(maximum SUV, SUV_{max})的下降率 $[\Delta\text{SUV}_{\text{max}}, \Delta\text{SUV}_{\text{max}}=100\% \times (\text{NAC前基线SUV}_{\text{max}} - \text{NAC第3个周期SUV}_{\text{max}}) / \text{NAC前基线SUV}_{\text{max}}]$ 。结果表明87例患者的平均 $\Delta\text{SUV}_{\text{max}}$ 为69.1%(范围为4.2%~100%), pCR组 $\Delta\text{SUV}_{\text{max}}$ 高于非pCR组,且 $\Delta\text{SUV}_{\text{max}}$ 与残留癌症负荷指数呈负相关($r=-0.408, P<0.001$)。Bulut等^[37]的研究共纳入31例乳腺癌患者共355张PET-CT图像,采用深度学习中的卷积神经网络模型预测NAC后pCR,取得了AUC值90%、准确度84%、灵敏度85%和特异度84%的预测效果。

PET-MRI是一种混合的成像技术,与PET-CT相比,它可以同时收集形态、代谢和功能参数,具有更高的对比分辨率^[38]。在Cho等^[39]的回顾性研究中,入组的26例乳腺癌患者分别在NAC前3周和NAC第1个周期完成后2周接受了PET-MRI检查,PET-MRI参数与病灶总糖酵解和MRI信号增强比的变化结合可以提高预测病理缓解的灵敏性和特异性。Choi等^[40]通过回顾性研究发现,采用深度学习中的卷积神经网络模型能够进一步提高PET-MRI预测NAC反应的准确性。

5 各种成像方式的局限性与挑战

对于接受NAC治疗的局部晚期乳腺癌患者,评估肿瘤残留和预测疗效对临床决策有重要意义。虽然各种成像方式在预测NAC疗效方面均有一定的价值,但仍有一些局限性和挑战。首先,与超声和乳腺X线摄影相比,MRI和PET检查耗时较长,成像速度慢,价格昂贵,且有一定辐射危害。其次,人工智能算法大多都是典型的“黑箱”模型,只知道输入与输出,不了解中间过程,很难以直截了当的方式解释它们的决策。最后,已发表的研究大多为回顾性研究,样本量小,且研究对象多为高收入国家人群,后续需要开展更多的前瞻性大样本研究,还应扩大数据的多样性,考虑从不同地域人群和人口群体中收集数据,以保证研究结果的适用性和可靠性。

6 成像技术的未来前景

成像技术的进步有望解决乳腺癌在筛查、治疗和预后等领域的诸多挑战。人工智能的最新进展

在量化医学成像方面取得了巨大进步。深度学习作为人工智能的子领域极具潜力,它主要通过学习样本数据的内在规律和表示层次,基于在学习过程中获得的信息对文字、图像和声音等数据进行解释,从而表现出类似于人类的学习与分析能力^[41]。Qu等^[42]开展的一项回顾性研究基于DCE-MRI数据,采用深度学习方法对NAC疗效进行评估,获得了AUC值高达0.970的预测效果。但深度学习常由于样本量不足难以支撑有效的训练,数据集的不一致和不平衡也会影响模型的泛化能力。此外,深度学习模型目前仍属于“黑箱”模型,仍然无法可靠地解释。为了应对这些挑战,可以利用半自动标注工具减轻标注负担,提高标注效率;探索迁移学习、集成学习、无监督学习等新的学习方法;研究和开发新的模型解释技术,如基于模型本身或基于结果的方法,提高模型的可解释性。在未来,仍需开展大规模、多中心、高质量的研究,以推动研究结果向临床应用的转化。

7 小结

NAC不仅已成为局部晚期乳腺癌的标准治疗方法,也在早期、可手术的乳腺癌患者中得到了广泛应用。本综述通过整合不同成像方式的参数指标、影像组学和人工智能相关文献,研究了各成像方式在NAC疗效预测中的价值,确定了有价值的参数指标和影像组学特征,特别是考虑到了不同的感兴趣区和模态的选择。虽然每种成像方式都有其优点,但DCE-MRI逐渐脱颖而出,成为了预测NAC疗效最准确的成像方式,这一结果在多项研究中得到了验证。对于有MRI禁忌的患者,CESM成为了可行且准确的替代方法。尽管面临数据有限等挑战,将不同成像方式、影像组学和人工智能协同仍可建立强大的预测模型,甚至有望改变乳腺癌的治疗方法。

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