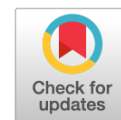


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Роль маммографии в радиомике рака молочной железы

В.Г. Говорухина¹, С.С. Семенов^{2, 3}, П.Б. Гележе², В.В. Диденко^{2, 4},
С.П. Морозов², А.Е. Андрейченко²

¹ Московский государственный университет имени М.В. Ломоносова, Москва, Российская Федерация

² Научно-практический клинический центр диагностики и телемедицинских технологий Департамента здравоохранения города Москвы, Москва, Российская Федерация

³ Московский клинический научно-практический центр имени А.С. Логинова, Москва, Российская Федерация

⁴ Городская клиническая онкологическая больница № 1, Москва, Российская Федерация

АННОТАЦИЯ

Маммография — в настоящее время единственный способ скрининга рака молочной железы (РМЖ). Хотя цифровая маммография служит основным и наиболее широкодоступным методом для выявления РМЖ, её эффективность в обнаружении и оценке внутриопухолевой гетерогенности опухоли ограничена. Пункционная биопсия не может отразить гистологической картины опухоли в целом из-за небольшого размера образца ткани или опухоли. По этой причине выбор подходящего лечения и определение прогноза становится затруднительным. В этом случае такой неинвазивный подход, как медицинская визуализация, даёт более полное представление об опухоли, перспективен при «виртуальной биопсии», а также в контроле прогрессирования заболевания и ответа на терапию.

Радиомика с помощью текстурного анализа позволяет взглянуть на снимок как на группу числовых характеристик, выйти за пределы привычного качественного зрительного восприятия интенсивностей и перейти к более глубокому анализу цифровых, пиксельных данных с целью повышения точности дифференциальной диагностики. Метод радиогеномики, являясь естественным продолжением радиомики, фокусируется на определении экспрессии генов исходя из лучевого фенотипа опухоли. В обзоре рассматриваются возможности применения маммографии в радиомике и радиогеномике РМЖ.

В статье представлен обзор литературы баз данных PubMed, Medline, Springer, eLibrary, а также найденных с помощью Google Scholar актуальных российских научных статей. Полученная релевантная информация объединена, структурирована и проанализирована с целью изучения роли маммографии в радиомике РМЖ.

Ключевые слова: рак молочной железы; маммография; радиомика; радиогеномика; искусственный интеллект.

Как цитировать

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The role of mammography in breast cancer radiomics

Veronika G. Govorukhina¹, Serafim S. Semenov^{2, 3}, Pavel B. Gelezhe², Vera V. Didenko^{2, 4}, Sergey P. Morozov², Anna E. Andreychenko²

¹ Lomonosov Moscow State University, Moscow, Russian Federation

² Research and Practical Clinical Center for Diagnostics and Telemedicine Technologies of Moscow Health Care, Moscow, Russian Federation

³ Moscow Clinical Scientific Center named after A.S. Loginov, Moscow, Russian Federation

⁴ City Clinical Oncology Hospital № 1, Moscow, Russian Federation

ABSTRACT

Mammography is still the only screening method for breast cancer. Although digital mammography is the most common and widely used method for detecting breast cancer, it is ineffective at detecting and assessing intratumoral heterogeneity. Due to the small size of the tissue sample or tumor, biopsies often fail to represent the entire tumor. For this reason, selecting a treatment and determining a patient's prognosis becomes difficult. In this case, medical imaging is a noninvasive approach that can provide a more comprehensive view of the entire tumor, act as a "virtual biopsy," and be useful for monitoring disease progression and response to therapy.

Radiomics with texture analysis allows you to look at an image as a group of numerical data, moving beyond the usual visual perception and into a deeper analysis of digital, pixel data to improve the accuracy of differential diagnosis. Radiogenomics is a natural extension of radiomics that focuses on determining gene expression based on radiologic tumor phenotype. The purpose of this review is to evaluate the role of mammography in breast cancer radiomics and radiogenomics.

The article presents a literature review of relevant Russian scientific articles found in databases such as PubMed, Medline, Springer, eLibrary, and Google Scholar. The information obtained was then pooled, structured, and analyzed to examine the role of mammography in breast cancer screening radiomics.

Keywords: breast cancer; mammography; radiomics; radiogenomics; artificial intelligence.

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乳房造影检查在乳腺癌放射学中的作用

Veronika G. Govorukhina¹, Serafim S. Semenov^{2, 3}, Pavel B. Gelezhe², Vera V. Didenko^{2, 4},
Sergey P. Morozov², Anna E. Andreychenko²

¹ Lomonosov Moscow State University, Moscow, Russian Federation

² Research and Practical Clinical Center for Diagnostics and Telemedicine Technologies of Moscow Health Care, Moscow, Russian Federation

³ Moscow Clinical Scientific Center named after A.S. Loginov, Moscow, Russian Federation

⁴ City Clinical Oncology Hospital № 1, Moscow, Russian Federation

简评

乳房造影检查是目前筛查乳腺癌的唯一方法。尽管数字乳房x线照相术是检测乳腺癌的主要和最广泛可用的方法，但其在检测和评估肿瘤的肿瘤内异质性方面的有效性有限。由于组织样本或肿瘤体积小，穿刺活检不能反映整个肿瘤的组织学图片。由于这个原因，选择适当的治疗方法和确定预后变得复杂。在这种情况下，医学成像这样的非侵入性方法给出了肿瘤的更完整的画面，是有希望的»虚拟活检«，以及用于监测疾病的进展和对治疗的反应。

使用纹理分析的放射学允许您将图像视为一组数值特征，超越通常的定性视觉感知强度，并继续深入分析数字，像素数据，以提高差分诊断的准确性。放射基因组学方法是放射组学的自然延伸，侧重于根据肿瘤的放射表型确定基因的表达。该综述探讨了在乳腺癌的放射组学和放射基因组学中使用乳房造影照相术的可能性。

本文概述了PubMed, Medline, Springer, eLibrary数据库的文献，以及使用Google学术搜索找到的相关俄罗斯科学文章。将获得的相关信息组合，结构与分析，以研究乳房造影照相术在乳腺癌放射组学中的作用。

关键词： 乳腺癌; 乳房x光检查; 放射学; 放射基因组学; 人工智能。

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乳腺癌：相关性、特征

乳腺癌(BC)是现代肿瘤学的一个热点问题,因为它在女性恶性肿瘤中的发病率最高[1]。2018年俄罗斯每10万女性人有89.8例乳腺癌发病[1],2019年共检出乳腺癌73366例,其中III、IV期比例为27.7%[2]。

BC是一种异质性疾病,这有不同的状态知道RMG的受污染,形态类型和表达类型亚之间的差异[3, 4]。乳腺癌受体状态包括雌激素受体(estrogen receptors, ER)、孕激素受体(progesterone receptors, PR)和人类表皮生长因子受体2(human epidermal growth factor receptor 2; HER2)的表达。增殖标志物Ki67的免疫化学染色和表皮生长因子受体(epidermal growth factor receptor, EGFR),而用于确定乳腺癌的分子亚型[4]。

乳腺癌有5种分子亚型:

- 1) 苯巴比妥 A [ER+, PR+ 高($\geq 20\%$), HER2-, Ki-67 低($\leq 20\%$): 雌激素依赖性侵袭性肿瘤; 没有HER2蛋白受体的过度表达; 以ER基因高表达为特征;
- 2) 苯巴比妥 B [ER+, PR+ 低($\leq 20\%$), HER2-, Ki-67 高]: 雌激素依赖性肿瘤; 没有HER2蛋白受体的过度表达;
- 3) 巴比妥 B [ER+, HER2+, Ki-67 水平任何, 任何 PR]: 雌性气泡倾向性肿瘤性; 表达了HER2 癌基因的特征; 表达了ER 基因的表达;
- 4) HER2 阳性 [ER- 和 PR-, 任何Ki-67, HER2+]: 不依赖雌激素的侵袭性肿瘤; 表达HER2癌基因的扩增;
- 5) 三阴性(基底样): 生存率最差的雌激素非依赖性侵袭性肿瘤(ER-, PR-, HER2-) [3-5]。

众所周知,肿瘤生物学会影响治疗的选择,以及预后的预后: ER+和PR+患者的无病生存期更长,而三阴性乳腺癌(TNBC)(ER-, PR-, HER2-)的存活时间更长。最具侵略性的课程和最差的存活率[3, 6]。由于对疾病的更准确诊断,使用生物标志物来识别乳腺癌亚型可提高患者的存活率。例如,肿瘤中有ER和PR表达的患者应该接受内分泌治疗; 当HER2 表达时,抗HER2 治疗[7]。

瘤内异质性是同一肿瘤内各组细胞的形态结构异质性和各种标志物表达的变异性[8, 9]。肿瘤内形态异质性可以描述为肿瘤不同区域的差

异,即空间异质性,或随着时间上的肿瘤进展-时间上的异质性[8]。由于肿瘤的这种异质性,以及由于穿刺组织样本的体积小,活检不能反映整个肿瘤的组织学图片。由于这个原因,选择适当的治疗方法和确定预后变得复杂。如果肿瘤体积小,活检也很困难。这种情况下,医学成像这样的非侵入性方法给出了肿瘤的更完整的画面,是有希望的”虚拟活检”,以及用于监测疾病的进展和对治疗的反应[7, 10-12]。

乳腺癌的早期诊断, 治疗结果的预测

早期发现癌症是降低女性死亡率的有效方法[13]。乳房X光检查方法是手机和诊断诊断的唯一方法 [10]。尽管X乳房光是早期的诊断数字结果,主要的检测结果,但其检测的有效性方法是有限的(ACR-C和D) [14]患者 X 乳房 X 光检查的可能性较低,因为有可能是纤维结构疾病形成的图像重叠 [15, 16]。虽然还有一组患者的某些部分下降了,但在诊断某一部分具有最佳的后期和怀疑组合,这两个指标的差异分别在75-90%和80-90%之间 [15]。O. Demircioglu和合著者 [17]渗入图像分析的人工智能(AI)技术的最新进展对肿瘤检测和医生诊断具有诊断、诊断治疗和监测进展情况 [6, 15, 17]。

渗入图像分析的人工智能(AI)技术的最新进展对肿瘤检测和医生诊断具有诊断、诊断治疗和监测进展情况 [6]。然而,在乳腺癌中早期确定疾病的预后和预测对治疗的反应是临床实践和研究的核心任务。这个角度出发,利用气候分析确定癌症亚型并预测治疗反应的人工智能的其他表现是开放的 [6, 18, 19]。

对乳房X光检查的分析 包括X光医生对肿瘤结构及其与周围组织关系的解释、微泡泡的位置和结构特征。创造真正个性化的治疗还需要进行教育教育[6]。

肿瘤内异质性对于癌症的准确诊断、临床预后(对治疗的反应、生存、疾病进展等)和治疗很重要[20, 21]。早期发现的肿瘤对治疗的恢复力来说,对于改善结局来说,这将成为即时改变治疗方案的可能 [6]。

因此,需要提高检测、预测结果和对乳腺癌治疗

的反应的效率。 一组结合放射组学和放射基因组学的特殊技术作为一种工具正在获得动力，以最大化可以从几乎任何数字医学成像模式中提取的信息[15]。

放射组学和放射基因组学

射线诊断图像包含反映病理生理过程的信息，通过图像定量分析可以揭示这种相互关系[22]。换言之肿瘤在细胞和基因水平上的特征反映在肿瘤的表型模式中，这些模式可以在图像中表现和发现[23]。

放射组学是一个由多维数据的准备和随后的定量分析阶段组成的过程，从数字医学图像中提取的图像(Omik后缀出现在专门研究大量数据的分子生物学分支的名称中[24])。放射组学被描述为利用特定算法对图像进行分析，旨在提取图像的数值特性，目的建立分类模型，完善医疗决策支持，确定疾病预后和[25, 26]治疗，[27]这对个性化治疗特别有价值。放射学中有一个图像感兴趣的区域被用来产生一组(有时几十个和几百个)的数值特征，每一个都可能包含一个特定的理论信息方面(通常称为“放射特征”)，在普通图像查看器中是不可用的[15]。放射学中使用数字医学图像的自动纹理特征提取算法将医学成像数据转换为有序统计数据集[28]。换句话说，借助理分析的放射组学使您可以将图像视为一组数值特征，超越通常的视觉感知并进行多维数据的分析。

放射基因组学是一种在患者基因型和成像表型之间建立联系的技术。 需要注意的是，“放射基因组学”一词也可以用来指遗传变异及其与放射治疗反应的关系[29, 30]，但更常用于评估肿瘤或某种疾病的影像特征与其基因表达样本和基因突变之间的关系[25, 26]。

放射基因组学方法允许根据肿瘤的放射表型确定肿瘤中基因的表达。这一点很重要，因为肿瘤是异质的，放射数据是从整个感兴趣的区域(肿瘤)中提取的，而不是从单个样本中提取的[22]。放射基因组学还可以评估对治疗的反应，而不仅仅是基于对肿瘤大小的传统测量[25]。放射组学和放射基因组学的结合将导致检测图像中的基因异常 [6]。放射组学和放射基因组学通过识别不同类型临床数据之间的关系来提高临床诊断的准确性并具有预测价值[22]。

放射学阶段

将放射组学视为一个过程，可以区分几个主要阶段：图像采集； 突出感兴趣的领域； 从感兴趣区域中提取放射学特征(图像的纹理分析)； 使用获得的放射学数据分析纹理特征并构建各种预测和分类模型，并可选择包括附加信息(例如，临床、人口统计学或基因组数据；合并症的存在)[22, 23, 31]。图1上放射组学的阶段被证明，下面描述了它们更详细的特性。

1. 临床问题识别和**数字医学成像**，不包括低质量研究。

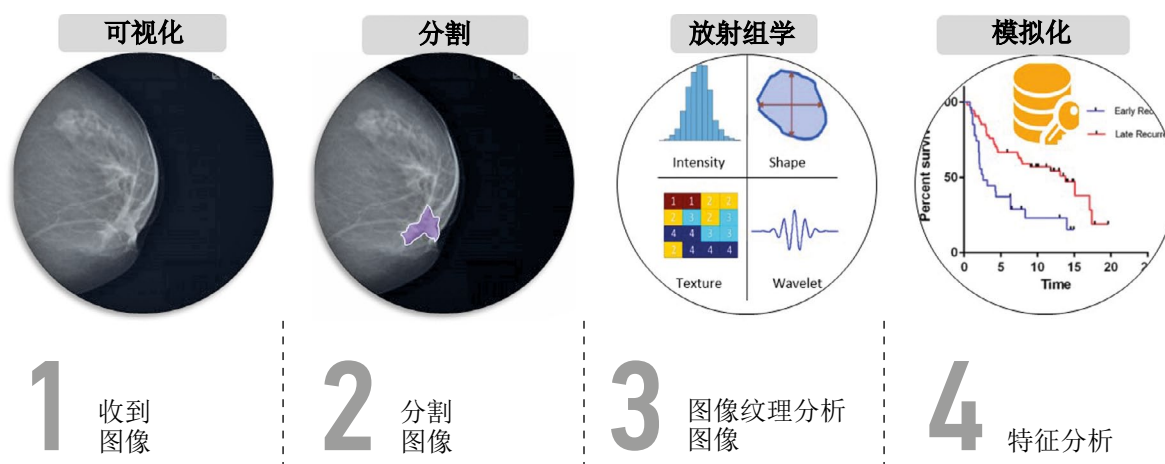


图 1图显示了放射组学的典型步骤。 获得医学图像后(1)，它们被手动或自动分割(2)。 使用特殊软件或编程语言模块(3)从分割的感兴趣区域中提取一阶和更高阶的放射学特征。 接下来，对获得的纹理特征中最重要的进行分析和选择。最后阶段，基于分析的放射组学数据，构建分类或预测的各种临床和诊断模型(4)。

2. **将图像分割**为感兴趣的主要研究区域[32], 例如恶性肿瘤以评估其肿瘤内异质性。许多肿瘤的边界模糊, 这使得其分割的可重复性具有挑战性[33]。最好使用半自动或全自动的特殊软件选择感兴趣的领域。然而, 在某些情况下, 需要专家的澄清和手动分配[23, 34]。选择感兴趣区域的过程不是标准化的, 感兴趣区域可以包含整个肿瘤及其部分[35, 36]。由于不同的放射科医生对图像的解释不同, 人工识别兴趣区域既费时又多变, 这最终影响了所建放射模型的准确性, [33]但现代大数据深度学习技术能够将这种影响降至最低[37]。

3. **使用数学运算从图像中**像素或体素的强度和相对位置的数值进行数学运算, 从分割的感兴趣区域中提取各种放射组学特征。提取的定量特征分为形态特征(体积和形状)、直方图特征(灰度水平强度描述)二阶或更高阶[26, 34]。形态特征反映了兴趣区域的形态。对于平面图像, 二维形状特征是相关的, 例如, 周长与曲面的比值和圆度是感兴趣区域形状与圆形状近似的度量。因此星状肿瘤的表面积与体积之比将大于圆形肿瘤[31]。

一阶直方图特征反[38]映了兴趣区像素的灰度水平强度分布。这一类最常见的特征一平均值和中值一表明强度范围的宽度; 熵是强度分布

不均匀性的度量(较高的值对应于较不均匀的区域)[39]。然而, 一阶统计特征并不反映像素的空间位置。

二阶直方图特征[38]也就是所谓的纹理特征, 反映了两个相邻像素之间具有相同或不同亮度值的空间关系。最常用的纹理特征提取方法是使用灰度水平的联合匹配矩阵, 灰度水平共轭矩阵(gray level co-occurrence matrix, GLCM)是一个矩阵, 其行数和列数反映灰度水平的值; 矩阵单元反映了灰度值在特定关系中的次数(分析像素之间的角度和距离)。例如, 使用这种矩阵得到的特征包括表示异质性的二阶熵; 描述图像均匀性的能量; 对比度, 定义强度的局部变化[10]。放射组学中纹理分析提供了有关测量肿瘤内异质性的信息[22, 40]。

在图2为一阶和二阶直方图特征的对比, 展示了灰度级邻接矩阵的形成: 图2(a)为两幅原始图像, 2(b)为一阶直方图; 在图2(c)为原始图像获得灰度邻接矩阵。这些矩阵的行和列标题包含灰色数字的阴影。每个单元格都包含水平像素对的数量, 其中该单元格行列标题中带有阴影的像素相对于彼此成 0° 角[41]。随后, 数学算法根据所获得的强度直方图和灰度邻接矩阵计算一组放射组学特征以进行分析和建模。

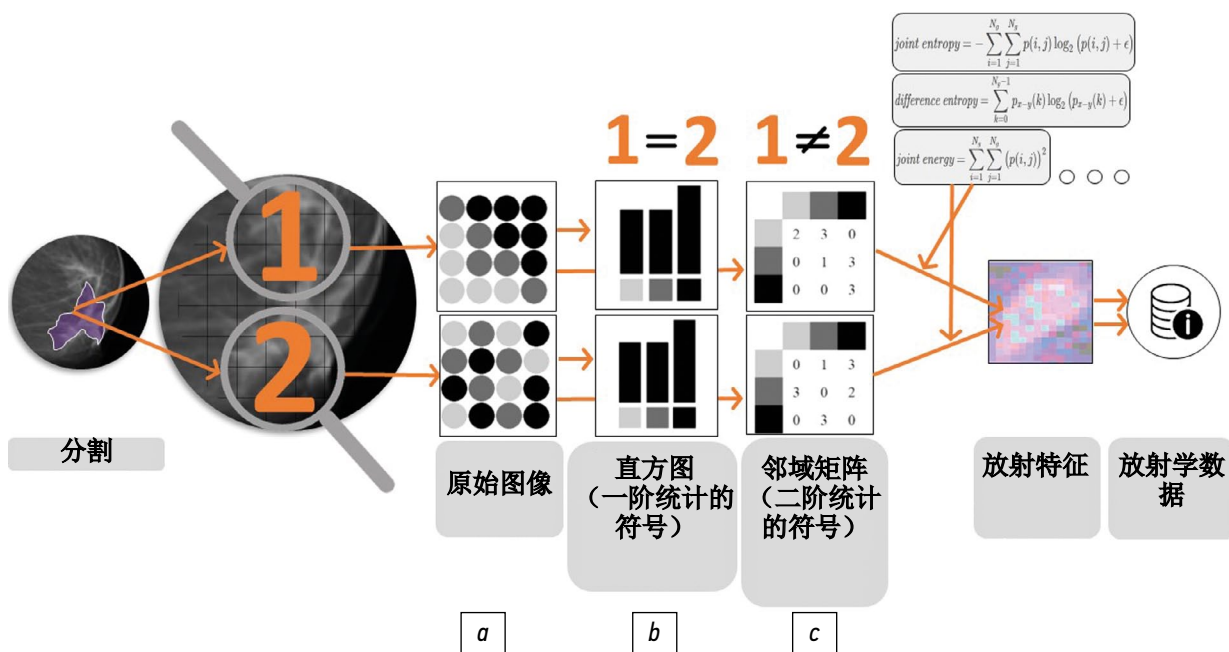


图 2 一阶和二阶直方图特征的比较。分割图像 (a) 的两个不同的原始 ROI 包含相同数量的浅灰色、深灰色和黑色像素。基于某些阴影的像素数(一阶直方图特征)的亮度直方图是相同的(b)。这些特征不反映像素的相对位置。邻接矩阵(二阶直方图特征)反映了图像的异质性(c)。随后, 数学算法根据所获得的强度直方图和灰度邻接矩阵计算一组放射组学特征以进行分析和建模。

4. 分析和建模: 根据提出的问题, 获得的放射学特征可以通过各种方式进行分析—从统计模型到机器学习方法。

鉴于从图像中提取的大量数据, 第一阶段是选择或减少特征。不可复制的特征应该排除, 因为它们很可能导致构建模型的错误结果[42, 43]。第二阶段是多维数据分析[31]和三个主要群体的模型, 即预测、解释和描述[15]。描述性模型用于获得每个特征的总体图, 总结其主要特征。例如, 通常用于生物医学数据的解释方法侧重于模型建立特征与结果之间关系的能力, 例如灰度重合矩阵的纹理特征与乳腺癌形态类型之间的关系感兴趣的区域内。预测模型的形成是通过机器学习方法进行的: 这些模型根据所获得的输入数据分析特定结果的概率, [15]例如, 用于预测对新辅助乳腺癌化疗缺乏反应的放射组学模型。临床环境中使用前所得模型结果的质量和再现性应该受到赞赏[31]。

经验、机会和前景在乳腺癌的放射组学和放射基因组学应用乳房X光检查。

识别恶性肿瘤

乳房 X 光检查中最困难和重要的一步是将乳房 X 光检查结果分为良性和恶性的划分[44]。在 N.Mao和合著者[45]已经证明与人工智能一起使用定量标志物可以在使用乳房X光检查时提供更高的诊断效率, 而不是执行效率由经验丰富的放射科医生诊断[15]。

对放射科医生来说, 图像将微钙化归因于良性或恶性过程的过程是难的问题[46]。目前在检测到潜在数量减少的可疑方解石时, 可以结合人工智能方法对图像进行纹理分析不必要的活检[47, 48]。

乳腺实质的特征可能反映了乳腺癌的生物学危险因素。H. Li 和合者[49]表明使用从受影响和对侧(具有正常实质)腺体的乳房 X 线照片中提取的纹理特征, 可以提高数字乳房 X 光检查在乳腺癌诊断中的准确性。研究表明高灵敏度和特异性的放射学可以将乳腺恶性肿瘤从良性分类[50]。

确定乳腺癌亚型的

近年来的放射基因组学研究证实了乳腺癌成像的MR特征与分子亚型(发光A、发光B、HER2和TNRMF)的相关性[51]。虽然从乳房X光片图像中可以得到的信息比磁共振成像(MRI)时少, 但目前有一些研究, 展示了乳腺癌造影在射电和射电基因组学中的潜力。在W. Ma和合著的研究[10]显示了通过从乳房摄影图像中提取放射学特征来预测乳腺癌分子亚型的可能性。最重要的特征是: 圆度、凹度、灰度平均值和相关性。结果表明发光体和TNRMG具有特殊的纹理特征, 与其他亚型不同, 这使得它们可以通过放射学进行定量区分。

某些腺癌患者中, 使用新辅助化疗不能产生有效的治疗反应, 导致手术延迟, 预测不好, 治疗费用增加。结果表明与独立的临床危险因素(如KI-67指数, HER2状态)改善新辅助化疗无应答预测模型[52]。

通过医学成像及早发现一种更具侵袭性的乳腺癌亚型, 即 TNBC, 将使医生能够在最终活检确认之前开出治疗方案 [53]。在 H.X.Zhang和合著的研究[53]与其他亚型相比TNBC 具有更大的圆度和凹度; ROC 曲线下面积(Receiver Operating Curve; 经典 ROC 曲线: 敏感性对特异性的依赖性图[54])用于评估这两个迹象在区分 TNBC 与其他乳腺癌亚型方面的准确性, 并且超过0.70[5355]。本研究中所有亚型的偏度系数(反映值分布相对于均值的偏度的直方图特征)均小于0(负偏度或左侧偏度)。结果表明TNBC 的不对称系数值低于其他研究亚型的系数。因此, 上述放射组学特征可以被认为是未来 TNBC 与其他 腺癌亚型之间差异的潜在标志[53]。

预测乳腺癌的发展和个性化筛查的可能性

基于放射组学的技术将有助于推进个性化筛查, 即 通过创建个人风险评估工具并将其纳入乳房 X 光检查的决策支持工具以及个人筛查间隔, 为患者制定个人筛查计划 [56-58]。众所周知, 较高的乳房密度与较高风险发展乳腺癌[59]。术语“密度”是指 X 射线穿过腺体时的衰减程度, 并反映纤维腺组织的分布。然而, 仅凭密度的定义并不能反映腺体结构的整体复杂性。图像衍生的纹理特征已被建议作为实质变化的标志, 表明与乳腺癌发展的联系[57, 59]

。D. Kontos 和合著的研究[59] (2019) 确定了放射组学表型,反映了乳房 X 线照片上实质的复杂性(除了密度之外),并且与乳腺癌具有独立的关系。与通常的密度定义不同,纹理特征反映了几乎看不见的和更局部化的薄壁组织图案复杂性。乳腺密度在低和中等复杂性的薄壁组织表型中不同,但在其他表型中相似。有趣的是获得的关于具有高密度乳腺的女性中具有最低复杂性(薄壁组织复杂性)的表型数据,因为它们具有更高的同质性,而具有低和中薄壁组织复杂性的表型包括少量高密度图像[59]。

腋下淋巴结转移的术前测定

乳腺癌转移最常见的部位是腋窝淋巴结。腋窝淋巴结状态是评估乳腺癌患者总体生存和无病生存的重要因素 [60]。术前准确确定腋窝淋巴结状态,可为医生提供信息,解决是否需要清扫淋巴结和预约辅助治疗的问题。目前通过观察淋巴结活检确定病情,可导致并发症,特别是血管损伤,神经和淋巴瘤的发展;而用影像学方法诊断的灵敏度较低[60]。在和合著的研究[60]开发了一个模型,其中包含从乳房 X 光照片中提取的放射学特征,当结合额外的临床和病理信息时,可以作为一种非侵入性方法,用于术前确定腋窝淋巴结转移。

对放射学应用的限制

尽管放射组学和放射基因组学在个性化医疗发展方面具有巨大潜力,但这些技术需要在独立数据集上进行验证,以确认其诊断和预测价值。这些技术在癌症研究中获得显著的实用价值需要时间,在开始应用于临床实践之前还需要更多的时间。这些限制是由于可用的大量数据目前不包含患者的全部特征[6]。放射组学结果可重复性的复杂性与其每个阶段的缺点有关:在不同的设备和可视化协议上获得不同的纹理特征[61, 62];手动肿瘤分割的黄金标准是耗时且依赖于操作者的;[63]减少可变性的半自动和自动分割未标准化;[64, 65]纹理特征之间存在明显的重复,导致需要减少数据的大小;[66, 67]放射组学的单位(纹理的基本单位)和人体组织之间的关系是什么,没有明确的解释。基本理论不明确、技术方法不规范的情

况下,任何“有意义”的研究成果都必须重新考虑[68]。

乳腺癌放射学中使用磁共振成像的前景

确凿的证据表明,乳腺MRI在诊断精度上优于传统的诊断方法,如乳腺造影[69]。除了*in situ* 检测到更多的导管癌外,乳腺 MRI 还经常改变肿瘤过程的阶段,这有助于优化治疗过程。

研究发现,从乳腺 MR 图像中提取的放射学征象反映了肿瘤的异质性、其血管化[70],并使区分导管癌与良性病灶成为可能[71]。现有的放射学模型在鉴别诊断良恶性病变的曲线下面积 (AUC) 方面仍落后于专业乳腺专家[72]。然而,在使用弥散加权成像放射组学识别可疑 (BI-RADS 4 和 5) 病变方面已显示出有希望的结果[73]。

放射组学似乎有助于指导临床决策,可能避免侵入性腋窝干预。两项不同的研究表明,放射模型能够预测观察淋巴结的转移[74, 75],这在临床上具有巨大的意义。

放射组学的另一个应用与 Ki-67 增殖指数有关,该指数用作乳腺癌的预后标志物[72]。最近的研究调查了使用一系列动态对比度增强的放射组学预测增殖标志物 Ki-67 表达的可能性 [76-79]。

结论

放射学的一个关键概念是射线诊断图像包含的数据可以提供比以前认为的更多的兴趣领域信息。乳房X光检查是早期腺癌检测的最有效方法。乳房X光照片可用于放射分析,可用于识别恶性肿瘤,确定腺癌亚型,预测疾病的发展和对治疗的反应。

基于放射组学的技术(如乳房 X 光检查)将来可能会被纳入医疗决策支持工具,以指导个体筛查、随访和可能的预防性治疗策略。然而需要注意的是放射学处于早期发展阶段,在临床应用之前需要进行大量的研究。

利用放射照相技术进行乳房X光检查,可以获得有关腺癌的重要诊断和预测信息,这有助于减少对侵入性和往往难以执行的程序的需要。尽管基于放射组学的技术在不久的将来不会取代

活检, 但有待新的研究支持, 将放射组学和放射基因组学整合到临床实践中将是实现降低乳腺癌死亡率目标的重要且有前景的挑战。

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ОБ АВТОРАХ

* Семенов Серафим Сергеевич;

адрес: Россия, 127051, Москва, ул. Петровка, д. 24, стр. 1;
ORCID: <https://orcid.org/0000-0003-2585-0864>;
eLibrary SPIN: 4790-0416; e-mail: s.semenov@npcmr.ru

Говорухина Вероника Георгиевна;

e-mail: govorukhinaver@gmail.com;
ORCID: <https://orcid.org/0000-0002-1611-9618>;
eLibrary SPIN: 7038-8580

Гележе Павел Борисович, к.м.н.;

e-mail: gelezhe.pavel@gmail.com;
ORCID: <https://orcid.org/0000-0003-1072-2202>;
eLibrary SPIN: 4841-3234

Диденко Вера Владимировна;

e-mail: didenko@npcmr.ru;
ORCID: <https://orcid.org/0000-0001-9068-1273>;
eLibrary SPIN: 5033-8376

Морозов Сергей Павлович, д.м.н., профессор;

e-mail: morozov@npcmr.ru;
ORCID: <https://orcid.org/0000-0001-6545-6170>;
eLibrary SPIN: 8542-1720

Андрейченко Анна Евгеньевна, к.физ.-мат.н.;

e-mail: a.andreychenko@npcmr.ru;
ORCID: <https://orcid.org/0000-0001-6359-0763>;
eLibrary SPIN: 6625-4186

AUTHORS' INFO

* Serafim S. Semenov, MD;

address: 24-1 Petrovka street, 127051 Moscow, Russia;
ORCID: <https://orcid.org/0000-0003-2585-0864>;
eLibrary SPIN: 4790-0416; e-mail: s.semenov@npcmr.ru

Veronika G. Govorukhina, MD;

e-mail: govorukhinaver@gmail.com;
ORCID: <https://orcid.org/0000-0002-1611-9618>;
eLibrary SPIN: 7038-8580

Pavel B. Gelezhe, MD, Cand. Sci. (Med.);

e-mail: gelezhe.pavel@gmail.com;
ORCID: <https://orcid.org/0000-0003-1072-2202>;
eLibrary SPIN: 4841-3234

Vera V. Didenko, MD;

e-mail: didenko@npcmr.ru;
ORCID: <https://orcid.org/0000-0001-9068-1273>;
eLibrary SPIN: 5033-8376

Sergey P. Morozov, MD, Dr. Sci. (Med.), Professor;

e-mail: morozov@npcmr.ru;
ORCID: <https://orcid.org/0000-0001-6545-6170>;
eLibrary SPIN: 8542-1720

Anna E. Andreychenko, Cand. Sci. (Phys.-Math.);

e-mail: a.andreychenko@npcmr.ru;
ORCID: <https://orcid.org/0000-0001-6359-0763>;
eLibrary SPIN: 6625-4186

* Автор, ответственный за переписку / Corresponding author