Роль системы контроля качества лучевой диагностики онкологических заболеваний в радиомике

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АННОТАЦИЯ

Современные методы медицинской визуализации дают возможность качественно и количественно оценить как ткани опухоли, так и пространство вокруг неё. Прогресс в информатике, особенно с участием методов машинного обучения в анализе медицинских изображений, позволяет преобразовывать любые радиологические исследования в поддающиеся анализу наборы данных. Среди этих наборов данных затем можно искать статистически значимые корреляции с клиническими событиями, чтобы впоследствии оценивать их прогностическую значимость и способность предсказывать тот или иной клинический исход. Эта концепция впервые была описана в 2012 г. и получила название «радиомика». Особую значимость она представляет для онкологии, поскольку известно, что каждый тип опухоли может подразделяться на множество различных молекулярно-генетических подтипов, и просто визуальной характеристики сейчас уже недостаточно. А радиомика при абсолютной неинвазивности способна обеспечить врача-радиолога информацией, которую порой может дать только гистологическое исследование биопсийного материала. Однако, как и в любой методике, основанной на использовании больших данных, здесь остро встаёт вопрос о качестве исходной информации данных, потому как это прямым образом может повлиять на исход анализа и дать неверную диагностическую информацию.

В литературном обзоре мы анализируем возможные подходы к обеспечению качества исследований на всех этапах — от технического контроля за состоянием диагностического оборудования до извлечения маркеров визуализации в онкологии и вычисления их корреляции с клиническими данными.

Ключевые слова: радиомика; лучевая диагностика; контроль качества; стандартизация; опухоли; онкологические заболевания.

The role of the quality control system for diagnostics of oncological diseases in radiomics

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ABSTRACT

Modern medical imaging methods allow for both qualitative and quantitative evaluations of tumors and issues surrounding them. Advances in computer science and big data processing are transforming any radiological study into analytic datasets, especially with the use of machine learning in medical image analysis. Among these datasets, statistically significant correlations with clinical events can then be searched for to subsequently assess their predictive value and ability to predict a particular clinical outcome. This concept, known as "radiomics," was first described in 2012. It is particularly important in oncology because each type of tumor can be subdivided into many different molecular genetic subtypes, and simple visual characteristics are no longer sufficient. Moreover, as an absolutely noninvasive method, radiomics can provide a radiologist with additional information that would otherwise be unavailable without a histological examination of biopsy material. However, as with any methodology based on the use of big data, the question of the quality of the initial data becomes critical, because this can directly affect the outcome of the analysis and provide incorrect diagnostic information.

In this literature review, we examine potential approaches to ensuring the quality of research at all stages, from technical control of the state of diagnostic equipment to the extraction of imaging markers in oncology and the calculation of their correlation with clinical data.

Keywords: radiomics; radiology; quality assurance; quality control; tumors; cancer; standardization.

肿瘤疾病放射诊断质量控制系统在放射组学中的作用

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简评

现代医学成像方法可以定性和定量地评估肿瘤组织及其周围的空间。计算机科学的进步，特别是机器学习方法在医学图像分析中的参与，允许将任何放射学研究转变为可分析的数据集。在这些数据集中，可以寻找有统计学意义夫人相关性与临床事件，以便随后评估其预后意义和预测不同临床结果的能力。　　这个概念在2012年首次被描述并称为»放射组学»。这对于肿瘤学特别重要，因为已知每种类型的肿瘤可以分为许多不同的分子遗传亚型，而仅仅是视觉特征已经不够了。在绝对非侵入性的情况下，放射组学能够为放射科医生提供有时只有活检材料的组织学检查才能提供的信息。然而，正如在任何基于使用大数据的方法中一样，存在关于初始数据信息的质量的尖锐问题，因为这可能直接影响分析的结果并给出不正确的诊断信息。

在文献综述中，我们分析了确保各个阶段研究质量的可能方法 – 从诊断设备状态的技术控制到提取肿瘤学中的成像标记并计算其与临床数据的相关性。

关键词：放射学；放射诊断；质量控制；标准化；肿瘤；肿瘤疾病。

绪论

放射成像技术的进步扩大了其在肿瘤治疗过程中的作用，从诊断原发灶和检测转移到监测治疗反应和预测个体患者预后。然而，利用放射诊断技术对肿瘤进行简单的直观分析是不够的，因为每种类型的肿瘤都可以细分为许多不同的分子遗传亚型。因此，每一种疾病都需要自己的治疗和诊断方法。在这方面，从诊断学的角度来看，无线电技术可以起到很大的帮助。

放射组学不仅是对医学图像进行视觉分析的一个方向，而且是从医学图像中提取大量定量标志的一个方向，这将允许对肿瘤表型和受影响组织的其他病理特性进行更深入的分析和综合评估，评估肿瘤的生物学特性并预测对治疗的反应[1, 2]。例如，实体癌在时间和空间上是异质性的，这限制了基于侵袭性活检的分子分析的使用，但为医学成像提供了巨大的潜力，从而可以无创检测肿瘤内异质性[3-5]。

转向定量分析需要开发自动化和可重复的分析方法，从图像中提取额外的信息[6]。这里出现了初始数据的质量问题，因为这可能会影响分析结果并给出错误的诊断信息，这将影响检测到的指标的临床意义和患者的健康[7, 8]。

因此，这篇文献综述的目的是分析在所有阶段确保放射诊断研究质量的可能方法-从诊断设备状态的技术控制到提取肿瘤学中的成像标记物并计算它们与临床数据的相关性。

PubMed、GoogleScholar 和 eLibrary 数据库中进行了英文和俄文的文献检索。PubMed 和 GoogleScholar 搜索放射组学、癌症和肿瘤、标准化、质量保证或质量控制。

放射组学方法

图像采集

放射组学的第一步是使用放射诊断方法获取图像：磁共振成像 (MRI)、计算机断层扫描 (CT)、正电子发射断层扫描结合计算机断层扫描 (PET / CT)（图 1）。放射诊断方法提供有关组织的物理、动力学特性、新陈代谢等的各种信息，通常是补充信息。例如，可以使用解剖 MRI 或 CT 获得基于病理结构大小或体积的分析。灌注可以通过一系列动态 MRI 或对比增强 CT 扫描来确定。弥散加权 MRI 可用于评估组织微循环和评估细胞结构。利用PET/CT和氟脱氧葡萄糖可以测量葡萄糖代谢率等代谢变化。此外，在临床试验过程中，可能会提出其他额外的生物标志物[9, 10]。

历史上，成像设备已经被开发用于图像的主观解释，允许临床医生确定，例如，病变的存在和位置。随后的技术创新集中在提高图像质量、减少扫描时间或与处理机集成上。这些设备的主要目的不是以可重复的方式提供定量测量。通常缺乏标准化成像的协议。此外，重建参数可能存在较大差异。H. Kim 合著者[11]检查了重建滤波器对肺癌患者 CT 图像中识别的放射学特征的影响，并得出结论，这种关系具有统计学意义，重建设置不应互换使用。N. Ohri 合著者 [12]评估了
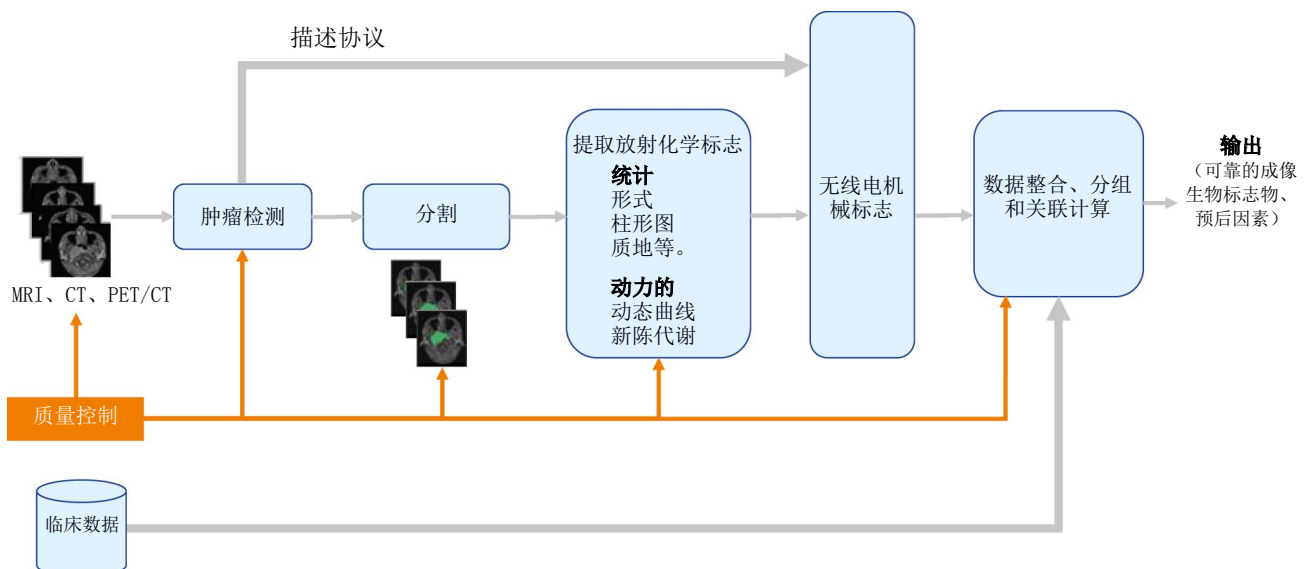

图 1放射诊断图像的放射组学分析图，说明质量控制系统的作用。

在各种数据收集模式、重建算法、后过滤和迭代次数下从 PET/CT 提取的放射学特征的可变性。结果表明50个特征中有40个具有显著的变异性，高达30%。在进行 MRI 时，由于扫描仪梯度磁场的幅度、所用的脉冲序列、造影剂注入的方法、k空间中轨迹的采样等因素，征象的变异性可能会发生更显着的变化 13]。由于数据的质量取决于临床中心使用的数据收集协议的可靠性，因此需要在未来的研究中仔细研究和分析这些变化对放射学体征稳定性的影响。

图像处理的新方法

放射特征释放的下一步是图像处理。因此，感兴趣区域（region of interest,ROI）和体积的识别是一项基本任务，例如，在肿瘤学实践中 [14]。由经验丰富的放射科医生或放射科医生手动描述被认为是金标准，但它是耗时的，并且具有高度的操作员之间甚至操作员内部的可变性。为了确定ROI，通常使用自动或半自动方法，例如阈值的确定、分类器、聚类、随机场的马尔可夫模型、人工神经网络、可变形模型以及其他一些方法[15]。

虽然自动化可以为标准化分割技术提供新的机会，但与复杂解剖结构或软组织低对比度区域相关的问题仍然存在，并且通常需要有经验的医生进行手动调整。允许避免错误的半自动分割方法之一是使用数字活检，其中仅基于强度和纹理值对某些片段进行采样[16]。对于图像的分割或选择，先进的机器学习方法也已经出现并被使用[17]。

有几个主要的倡议，旨在开发自动分割解决方案使用深度学习。例如，其中包括 Google DeepMind、Microsoft Project InnerEye、Mirada DLCExpert。这些自动分割工具已被证明可以提高结构重建的效率，尤其是对于有风险的器官 [18, 19]。在不久的将来，基于深度学习的细分工具可以变得足够可靠，用于常规研究。

特征提取、分组和数据集成

放射组学的主要阶段是提取多维数据集 – 放射组学特征 – 以量化图像中突出显示的感兴趣体积（ROI 或 VOI）[20]。从图像中提取的特征可以分为静态组和动态组。

静态特征的特征。 在一组静态特征中，区分了两类：形态学和统计[21]。形态特征用于定义三维（3D） 形状特征，例如体积和表面积，以及球形度（三维体积与球体的相似程度）。统计特征用于以数学方式评估 ROI 或感兴趣体积内的灰度分布。因此，一阶特征包括均值、标准差、百分位数、峰态和不对称性。它们用于表征强度的整体可变性。二阶特征通过分析 ROI 或区域内各个体素之间的关系来表征所选区域的纹理，即 显示本地分布。

动态特征的特征。 药代动力学模型通常用于量化一个区域（可能是一个或多个体素）内造影剂或其他指示剂的动态分布。通常，药代动力学模型将造影剂浓度视为 ROI 内动脉输入和残余造影剂衰减的函数。血管内和间质空间可以在不同的假设下建模。例如，最常用的动力学模型，托夫特模型，假设血管内和间质空间的对比度瞬间混合，而扩展的托夫特模型考虑了组织中对比物质浓度的延迟效应.绝热组织的均质模型是因为对比物质在血管外分布体积中的浓度变化比在血管内空间中的浓度变化要慢。因此，该模型假设对比物质从动脉相到静脉相的传递时间是有限的。

一般来说，现有的分析输送机通常包括数千个提取的放射特征，随着新数据的提供，这些特征的数量预计会增加。然而，临床上重要的特征将不包括所有突出的特征，而是与临床数据相关的最可靠的特征，以预测疾病的进展。

计算相关性，确定预后因素

和其他很多使用«-omics»后缀的领域一样，输入变量的数量往往远远超过患者的数量。为了减少误报的可能性，需要选择特定特征或缩小搜索区域的大小，常用基于过滤器的评分方法，如威尔科克森分析和主成分分析。这可以使用一维方法（当评估标准仅取决于对象的相关性时）或多变量方法（当使用加权和来最大化相关性并最小化冗余时）来实现 [22-25]。对象选择也可以与对象分类合并为一个模型。

一旦获得一组特征，就可以建立数据驱动的模型。这些模型包括受控和非受控方法[21,26]。非托管分析不提供结果变量，而是提供信息摘要。为了图形化显示，通常使用热图，在热图上同时识别数据矩阵中的簇结构。相反，监督分析创建的模型试图分解有关治疗结果的数据。

典型的分类方法包括传统的逻辑回归或更高级的机器学习方法。

与临床数据和分子分析结果密切相关的孤立放射组学特征可归类为成像生物标志物。而经典的生物标志物是通过肿瘤组织的组织学和分子检查获得的，即 通过侵入性方法，成像生物标志物允许对病理进行非侵入性表征。此外，它们是组织或肿瘤对任何干预反应的正常或病理过程的可靠指标。

放射组学参数的质量控制和标准化

为保证影像学特征的质量和成像生物标志物的可靠性，需要提高测量精度（图2），其由所获得数据的偏差或绝对误差的大小和数值的变异性决定（重复性和再现性，定义为测量值的分布）。

这些指标是通过在辐射诊断部门引入质量控制测试来实现的：验收、定期和内部控制（参数稳定性测试）[27]。验收测试在设备安装期间进行，以确定测试的特性符合制造商的限制值。如果参数得到确认，医疗机构的工作人员将首先对参数的稳定性进行测试，在此期间建立基础值以进行进一步的质量控制。内部控制或稳定性测试在质量控制系统中很重要，因为它可以预测诊断图像质量的恶化。俄罗斯定期测试包括监控扩展的参数列表，并由经认可的测试实验室进行。

国外的实践中，技术人员包括核磁共振、CT、PET/CT办公室。例如，医学物理学家在优化和标准化研究方面发挥着重要作用，他们还负责检查放射诊断设备的质量，并在进行研究时组织安全系统[28]。俄罗斯，目前不要求在放射诊断室工作人员中有这样的人员，医务人员缺乏必要的能力来进行放射检查。

必须采取措施确保放射诊断设备的质量控制，以实现可靠且临床可接受的测量重复性，这得到了北美放射学会 (Radiological Society of North America, RSNA)、欧洲放射学会 (European Society of Radiology, ESR) 等的支持。因此，作为定量成像网络 (Quantitative imaging Network, QIN; 美国) 和美国国家标准与技术研究院 (National Institute of Standards and Technology, NIST) 成员合作的结果，已开发出用于临床试验质量控制的体模 [29，30]。

作为放射组学分析的结果，发现的体征和临床数据之间形成关系，以检查构建的模型并评估输出信息的可靠性；对于新患者，它被验证[31，32]。使用文献数据、验证数据集上的测试或其他医疗机构的数据进行概括[31]。

研究方案的标准化

由于MRI、CT和PET/CT图像易受伪影和噪声的影响，因此有必要遵循标准的检查准备方法：排除扫描区域中导致畸变的异物；确保遵循既定的患者定位规则，以获得更好的视觉效果。病人应该长时间保持舒适而不移动。

此外，体素的大小和信号的强度对放射特征有很大的影响，因此，在设置扫描时，确保协议的标准化非常重要[32，33]。执行PET/CT和CT时，还应考虑重建滤波器对图像质量和信号强度的影响：应选择一个不会丢失有用信号的滤波器，并确保放射特征的高再现性[34]。

作为图像预处理的一部分，图像矩阵被缩放并缩减为各向同性（正方形）形式[35]。还建议将信号强度标准化为一个尺度，尤其是对于 MRI。为此，使用了统计方法，例如 ANTsR 和 WhiteStripe [36]。进行MRI时可能会出现信号强度不均匀的现象，这不是由组织的生物学特性引起的，而是由技术因素引起的。这种情况下，有必要纠正这种异质性，这应该包括在所执行程序的质量控制系统中。

后处理控制

后处理过程中，应使用经过验证的工作准确性的工具和算法[36]。例如，对于放射学特征的后续正确分析，重要的是在分割阶段使用高质量的工具。如果使用以前的半自动算法和人工分割校正，但现在出现了越来越多的基于人工智能技术的算法[37]，必须进行测试[38]。

孤立放射特征的监测和成像生物标志物的验证

这些研究的标准化和质量控制原则以及图像前后处理程序对于确保放射特征的质量（偏差和可变性）以及成像生物标记物的可靠性是必要的[39]。

这个阶段，质量控制工具被使用-幻影，这使得有可能评估偏差和再现性的提取特征。幻影既可以是数字的，也可以是物理的，它是用特定参

问题	无法进行鉴别诊断	**低测量精度来源：** 1）设备参数； 2）研究报告； 3）重建和后处理方法；等等 *ADC* 0.659±**0.434**
决定	提高测量精度	**监测指标：** 1）偏压； 2）变异性（重复性、再现性）
行动	质量控制	**质量控制体系：** 1）定制和定期质量控制 2）研究方案的标准化 3）用于准备患者和进行研究的统一方法 4）控制分割和数据分析
结果	获取生物标志可视化	确保高测量精度将使放射组学分析和可靠的成像生物标志物能够提高诊断价值 *ADC* 0.659±**0.216**

图 2在放射学中实施质量控制体系的理由。

数的物质制造的[40，41]。例如，对于乳腺癌的多中心研究，使用合适的模型，可以评估研究的可重复性和准确性[42]。

为了分析扫描参数的可变性、研究方法和后处理的影响，在不同条件下对模型进行重复扫描，然后计算测量值的可变性，并与阈值进行比较：欧洲药品管理局（EMA）建议设置不超过15%[39]。准确度是在研究模型或组织样本的过程中进行评估的，与比较地面真值和测量值的真实值时的相对误差相对应。验证成像生物标志物的过程中，建议将成功完成评估的阈值设置为15%[39]。放射组学的这一方向正在发展之中，在不久的将来可能成为诊断肿瘤和预测肿瘤过程的有效方法。我们相信，随着人工智能算法的引入，这一领域的研究数量将会增加，例如，在选定的体征和临床数据之间建立关系。然而，如果不在所有阶段实施所述的质量控制方法，就不可能获得可靠的数据，即在其他群体、其他设备上的可再现性，且指标偏差在规定限度内。诊断和远程医疗中心，人体模型先前被开发用于控制MRI（具有扩散指标）、CT（具有骨密度指标）的定量模式。从我们的观点来看，在这项工作中重要的是与技术专家（医学物理学家、工程师）和医务人员互动，开发具有特定测量精度

的模型，规划放射特征的研究，并进一步获得成像生物标志物。

成像生物标志物开发的作用

近年来，已经努力通过定义标准数据收集协议来改进标准化放射组学的方法。由国家癌症研究所（National Cancer Institute, NCI）创建的 QIN 以及 RSNA、定量成像生物标志物联盟（Quantitative Imaging Biomarkers Alliance,QIBA）和其他机构为此做出了特别努力。2010 年NCI启动了癌症研究所定量图像卓越中心(Cancer Institutee Centers for Quantitative Image Excellence)，国家临床试验网络（National Clinical Trials Network, NCTN）的创建一直是这项工作的重点[43]。定量图像改进中心正在创建PET/CT、CT和MR模型和标准化协议，QIBA就定量生物标记物成像测量的准确性以及达到这一精度水平所需的要求/程序提供了一致的决定[29、35、36、44、45]。

自从"放射组学"一词出现在科学文献中以来，已有数百项放射组学研究被发表，以提高诊断、治疗和预后的质量。越来越多的工作证明了成像

生物标志物作为临床决策的附加工具的价值，以及机器学习算法在这方面的作用[46]。

基于放射组学的方法的最早应用之一是在肺癌和乳腺癌的成像中成功地检测肿瘤。

乳腺癌是一种最常发生在全世界妇女身上的病理学。由于它是一种众所周知的异质性疾病，准确诊断和早期预测治疗反应是关键的临床实践[47]。有几项研究使用放射组学来预测乳腺癌的亚型或ER、PR、Ki67和HER2在钼靶摄影术[48]、PET/CT[49,50]和MRI上的状态[51,52]。除了乳腺癌的特征外，放射组学还可以提供一种预测前哨淋巴结转移的无创方法[53]。

大多数关于乳腺癌的放射学研究集中于评估对治疗的反应。H.M. Chan和合著者[54]开发了一种自动化的方法，用MRI预测早期乳腺癌患者对治疗无反应或反应不足。大多数其他研究中有人试图在新辅助化疗中获得完全形态缓解（pCR）的生物标志物。这是乳腺癌研究的热门话题。N.M. Braman和合著者[55]发现在动态增强MRI上发现的瘤内和瘤周特征可以在治疗前预测pCR。其他研究也表明 T1WI、T2WI 和 DWI 有助于检测 pCR [56，57]。

致力于乳腺癌预后的放射学研究正变得越来越普遍。H. Park 和合著者[58]开发了一种结合MRI 成像生物标志物和临床信息的算法，以单独评估乳腺癌患者的存活率。

肺癌是最危险的癌症类型，其患病率也在全球范围内持续增加。放射组学最重要的诊断应用之一是肺癌筛查。N. Nasrullah和合著者[59]提出了一种基于 LIDC-IDRI 数据集胸部 CT 研究的深度学习模型，在检测恶性肺结节方面取得了良好的结果，灵敏度为 94%，特异性为 91%。B.W.Carter和合著者[60]使用低剂量 CT 在国家肺癌研究 （NLST） 数据集中对诊断为肺癌的患者进行了筛查研究。对于在一年或两年内发展为恶性肿瘤的结节，他们分别获得了 80% 和79% 的预测准确率。

放射组学允许在术前阶段通过肿瘤结节转移（tumor nodules metastasis, TNM） 的转移来确定肺癌的分期 [61，62]，这对于做出手术干预的决定很重要。此外，该技术可用于检测肺癌的特定基因突变，例如EGFR基因的状态[63]，可以帮助医生选择最佳治疗策略。X. Fave和合著者使用δ放射特征预测III期非小细胞肺癌患者放疗期间的预后[64]。他们的结果表明，放射治疗引起的放射特征的改变将是肿瘤反应的指标。T.P. Coroller和合著者[65]研究发现晚期非小细胞肺癌患者术前CT影像学特征可预测新辅助放化疗后的异常反应。

近年来，放射组学越来越多地用于诊断、预测神经系统肿瘤[26,66,67]、头颈部肿瘤[68,69]、胃肠道肿瘤[70,71]、前列腺癌[72,73]和其他一些肿瘤疾病[74]的治疗反应和长期预后。

结论

肿瘤的早期发现和鉴别，肿瘤的异质性和表型特征对于患者分层，确定后续治疗方案和预测其疗效是非常重要的。诊断研究的放射分析提供了这方面的必要信息，但仅限于高质量收集和处理的数据。所有这些过程都需要使用各种质量控制方法进行标准化和优化，并且在从成像到成像生物标志物验证的每个阶段都需要进行。此外，为了确定生物标志物的预后意义，必须考虑临床信息，在此基础上寻找临床相关性。只有定性地满足所有这些标准，才能使生物标志物成像工具真正有用的医生和必要的病人。

附加信息

利益冲突。作者声明，没有明显的和潜在的利益冲突相关的发表这篇文章。

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