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Роль системы контроля качества лучевой диагностики онкологических заболеваний в радиомике

А.Н. Хоружая, Е.С. Ахмад, Д.С. Семенов

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

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.

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

Anna N. Khoruzhaya, Ekaterina S. Akhmad, Dmitry S. Semenov

Moscow Center for Diagnostics and Telemedicine, Moscow, Russian Federation

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.

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肿瘤疾病放射诊断质量控制系统在放射组学中的作用

Anna N. Khoruzhaya, Ekaterina S. Akhmad, Dmitry S. Semenov

Moscow Center for Diagnostics and Telemedicine, Moscow, Russian Federation

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的相关性与临床事件，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。

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INTRODUCTION

Advances in the field of radiation imaging significantly expanded their role in the entire range of methods for tumor processes management, from diagnosing primary foci and detecting metastases to monitoring treatment response and predicting individual patient outcomes. However, a simple visual analysis of tumor using radiation diagnostics is no longer sufficient, since each type of tumor is known to subdivide into many different molecular genetic subtypes. Accordingly, each tumor requires its own therapeutic and diagnostic approach. Here from the side of diagnostics, radiomics can be of great help.

Radiomics represents a method not just for visual analysis of medical images, but for large number extraction of quantitative signs, which allow deeper analysis and comprehensive assessment, such as tumor phenotypes and other pathological properties of affected tissues, as well as tumor biological characteristic assessment and treatment response prediction [1, 2]. For example, solid cancer is heterogeneous in time and space, which limits the use of molecular analysis based on invasive biopsy but offers great potential for medical imaging and enables non-invasive detection of intratumoral heterogeneity [3–5].

Quantitative analysis transition requires the development of automated and reproducible analysis methodologies to extract additional information from images [6]. Hence, a question in initial data quality arises, since this can affect the analysis outcome and provide incorrect diagnostic information, which will affect the clinical significance of detected indicators and patient health [7, 8].

Therefore, this literature review aimed to analyze possible approaches to ensure the quality of radiation diagnostics studies at all stages, from technical control over the state of diagnostic equipment to extracting imaging markers in oncology and calculating their correlation with clinical data.

Literature search was performed in the PubMed, GoogleScholar, and eLibrary databases in English and Russian languages. Requests such as “radiomics,” “cancer and tumors,” “standardization,” and “quality assurance or quality control” were used for PubMed and GoogleScholar.

METHODOLOGY OF RADIOMICS

Image acquisition

The step 1 in radiomics consists obtaining images using radiology methods, namely magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography combined with computed tomography (PET/CT) (Fig. 1). Radiology methods provide various and often complementary information about physical and kinetic properties of tissues, metabolism, etc. For example, analysis based on the size or volume of the pathological structure can be obtained using anatomical MRI or CT. Perfusion can be determined by a series of dynamic MRI or contrast-enhanced CT scans. Diffusion-weighted MRI can be used to assess tissue microcirculation and assess cellularity. Metabolic changes such as glucose metabolic rate can be measured using PET/CT and fluorodeoxyglucose. In addition, other additional biomarkers may be proposed in the course of clinical trials [9, 10].

Historically, imaging devices were developed for subjective interpretation of images, for clinicians to determine the presence of lesion and its location. Subsequent technical innovations are focused on image quality improvement, scan times reduction, or processing machines integration. These devices were not primarily intended to provide quantitative measurement in a reproducible manner. Standardization protocols for image acquisition are unavailable. In addition, significant differences may be present in reconstruction

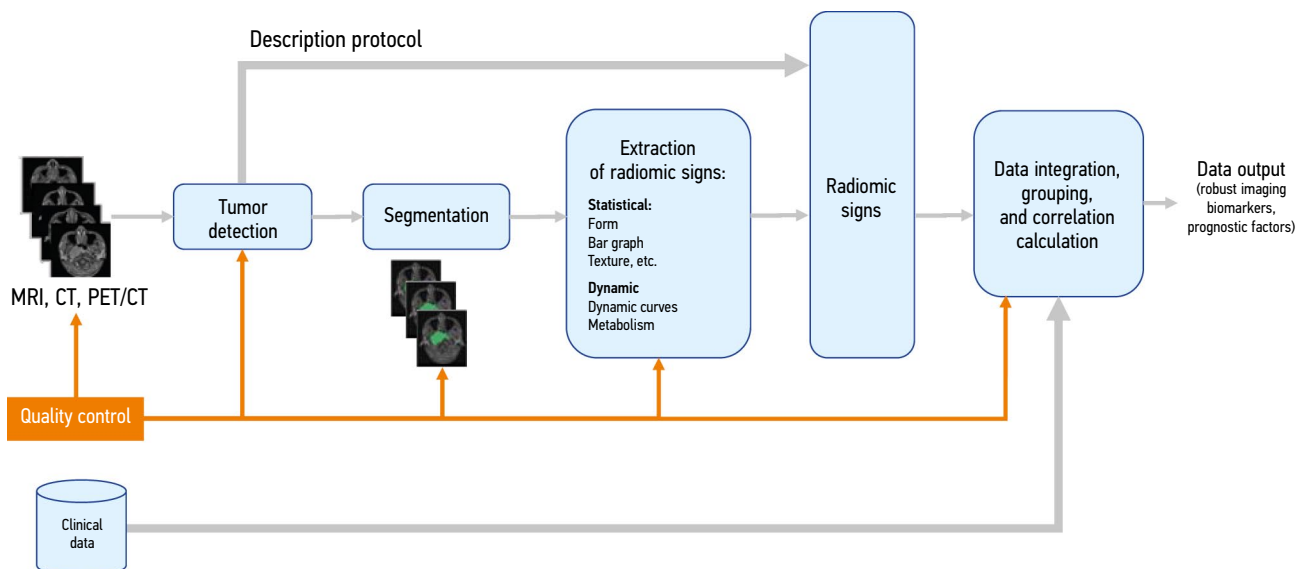


Fig. 1. Scheme of radiomics analysis of radiation diagnostic images indicating the role of quality control system.

parameters. H. Kim et al. [11] studied the effect of reconstruction filters on radiomic signs identified from CT images of patients with lung cancer and concluded that the relationship was statistically significant and reconstruction settings should not be used interchangeably. N. Ohri et al. [12] assessed the variability of radiomic characteristics obtained from PET/CT under different modes of data collection, algorithms reconstruction, post-filtration, and number of iterations. A total of 40 out of 50 signs were demonstrated to have significant (up to 30%) variability. Variability of signs can vary more significantly when performing MRI due to the amplitude of the scanner gradient magnetic field, used pulse sequence, contrast agent administration method, trajectory sampling in k-space, and other factors [13]. Data quality depends on reliability of data collection protocols used in clinical centers, thus the effect of these changes on the stability of radiomic signs needs to be carefully investigated and analyzed in future studies.

New methods of image processing

Image processing is the next step in radiomic signs extraction. Thus, identification of a region of interest (ROI) and volume of interest (VOI) is a fundamental task in oncological practice [14]. Manual description by experienced roentgenologists or radiologists is considered the gold standard, but is time-consuming with a high degree of inter- or even intra-operator variability. Automated or semi-automated methods are often used, such as determining threshold values, classifiers, clustering, Markov models of random fields, artificial neural networks, deformable models, and some others to determine ROI [15].

Automation can provide new opportunities for segmentation techniques standardization; however, problems associated with complex anatomy or areas of low soft tissue contrast are still present, therefore manual adjustments by an experienced physician are often required. One of the methods of semi-automatic segmentation, which avoids errors, is the use of digital biopsy, in which only certain segments are sampled based on intensity and texture values [16]. For segmentation or selection of images, advanced machine learning methods also emerged and used [17].

Several major initiatives aimed to develop automatic segmentation solutions using deep learning. These include, Google DeepMind, Microsoft Project InnerEye, and Mirada DLCEXpert. These automated segmentation tools showed to increase efficiency in structure reconstruction, especially for organs at risk [18, 19]. In the near future, deep learning-based segmentation tools may become reliable enough for routine research.

Extraction of signs, grouping, and data integration

Extraction of multidimensional datasets (radiomics signs) is the main stage of radiomics to quantify the VOI highlighted in the image [20]. Signs extracted from images can be divided into static and dynamic groups.

Characteristics of static signs. Static signs multitude comprises two categories, morphological and statistical [21]. Morphological signs are used to define three-dimensional (3D) shape characteristics such as volume and surface area, as well as sphericity (the extent a 3D volume resembles a sphere). Statistical signs are used to mathematically evaluate the distribution of grayscale within an ROI or VOI. Therefore, the first-order signs include the mean value, standard deviation, percentiles, kurtosis, and asymmetry, which are used to characterize the overall variability in intensity. Second-order signs characterize the texture of selected area by analyzing the relationship between individual voxels within the ROI or area, i.e., exhibit local distribution.

Aspects of dynamic signs. Pharmacokinetic modeling is commonly used to quantify the dynamic distribution of a contrast agent or other indicator within a region (which may be one or more voxels). In general, pharmacokinetic modeling considers the contrast agent concentration as a function of arterial input and residual contrast agent decay within the ROI. The intravascular and interstitial space can be modeled under different assumptions. For example, the most widely used kinetic model, the Toft model, assumes instant mixing of contrast in the intravascular and interstitial space, whereas the extended Toft model takes into account the effect of delayed contrast agent concentration in tissue. The model of homogeneity of adiabatic tissue is explained by the fact that contrast agent concentration in distribution volume outside the vessels changes more slowly compared to the intravascular space concentration. Thus, the model assumes a finite transit time for contrast agents from arterial phase to venous phase.

In general, existing analytical pipeline typically includes thousands of extracted radiomics characteristics, and this number is expected to grow with new available data. However, clinically significant signs include not all selected ones, but the most reliable signs, correlating with clinical data for the possibility of disease course prediction.

Calculation of correlations, identification of prognostic factors

As in many other fields where the -omics suffix is used, the number of input variables often far exceeds the number of patients. In order to reduce the probability of false positive results, specific sign selection or search area size reduction is required, and filter-based scoring approaches are commonly used, such as Wilcoxon analysis and principal component analysis. This can be implemented using either one-dimensional methods, when the evaluation criterion depends only on the object relevance, or multivariate methods, when a weighted sum is used to maximize relevance and minimize redundancy [22–25]. Object selection can also be combined with object classification into one model.

Once a set of characteristics is obtained, a data-driven model can be created. These models include controlled and

uncontrolled approaches [21, 26]. Unmanaged analysis does not provide a result variable, but rather a summary of information. Most often, a thermal map is used for its graphical display, on which cluster structures in data matrix are simultaneously detected. In contrast, in the course of monitored analysis, models are created, that attempt to divide the treatment outcome data. Typical classification methods include traditional logistic regression or more advanced machine learning methods.

Isolated radiomic signs that correlate closely with clinical data and molecular analysis results can be classified as imaging biomarkers, whereas classical biomarkers are obtained by histological and molecular examination of tumor tissues, i.e., using invasive method, imaging biomarkers provide non-invasive characterization of the pathology. In addition, reliable indicators of normal or pathological processes in tissues or tumor responses are available for any intervention.

QUALITY CONTROL AND STANDARDIZATION OF PARAMETERS IN RADIOMICS

Measurement accuracy improvement is necessary (Fig. 2) to ensure radiomic signs quality and imaging biomarkers reliability, which is determined by the magnitude of bias or absolute error of obtained data and variability of values (repeatability and reproducibility, defined as dispersion of measured values). These indicators are achieved

by introducing quality control tests in radiation diagnostic departments, namely acceptance tests, periodic, and internal control tests (tests for parameter constancy) [27]. Acceptance tests are performed during equipment installation to establish the compliance of tested characteristics with the manufacturer’s limit values. In case of confirmation of parameter conformity, the medical organization personnel perform the first tests for parameter constancy, during which base values are established for further quality control. Internal control or parameter constancy testing is essential in the quality control system as it predicts deterioration in diagnostic image quality. In Russia, periodic tests include monitoring of extended list of parameters, and are performed by certified testing laboratories.

In international practice, inclusion of technical personnel in the staff of MRI, CT, PET/CT offices is common. For example, a large role is assigned to medical physicists, whose important task consist research optimization and standardization, as well as radiation diagnostics equipment quality monitoring and safe system organization during research [28]. In Russia presence of such personnel in the staff of radiation diagnostics rooms are currently not required, and competencies to implement quality control for radiomics are unnecessary for medical personnel.

Measures to ensure quality control of radiological diagnostic equipment are required to achieve reliability and clinically acceptable repeatability of measurements, which is supported by the Radiological Society of North America (RSNA), the European Society of Radiology, etc. Thus, collaboration between members of the Quantitative Imaging

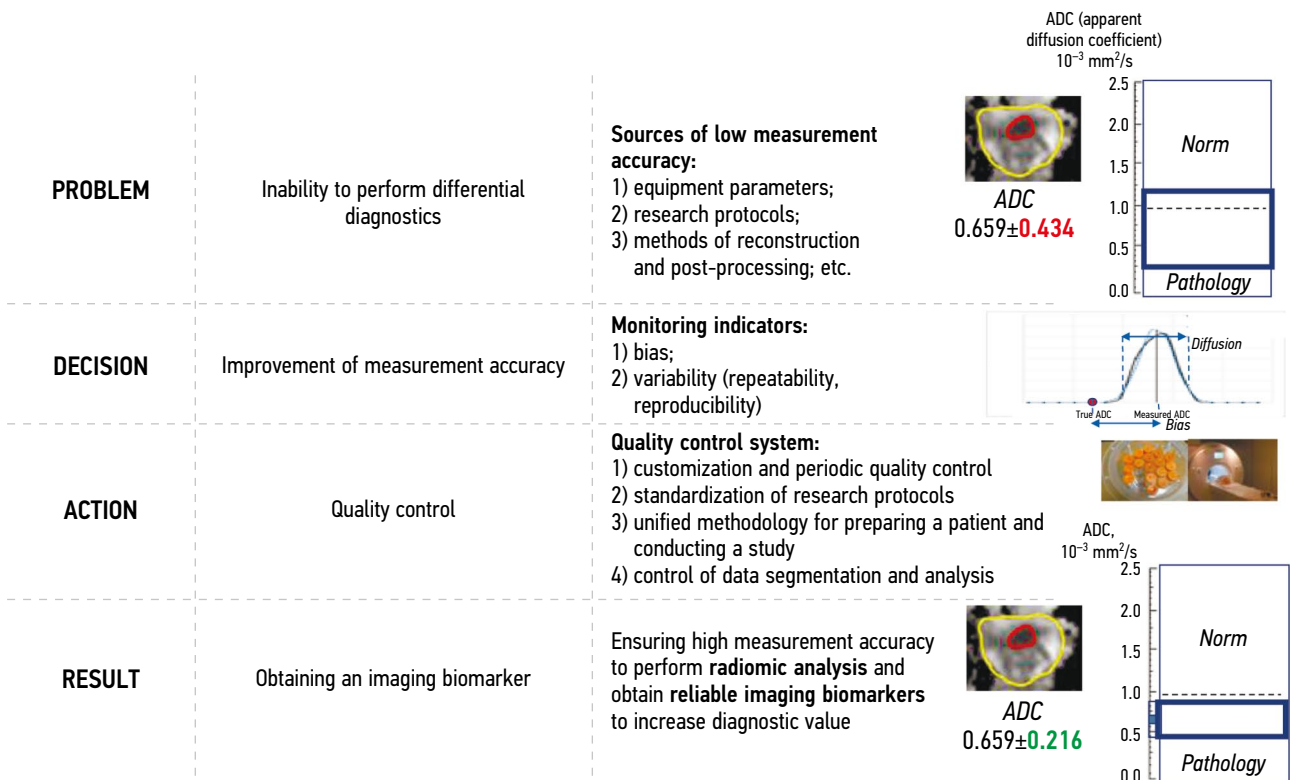


Fig. 2. Justification for quality control system implementation in radiomics.

Network (QIN; USA) and National Institute of Standards and Technology phantoms was developed for quality control in clinical trials [29, 30].

Relationships are formed between revealed signs and clinical data as a result of radiomic analysis to check the model constructed and assess output information reliability; it is validated for new patients [31, 32]. Literature data are used, as well as dataset validation testing, or data from other healthcare organizations to gain generalization possibility [31].

Standardization of study protocols

Following the standard methods of examination preparation, namely exclude foreign objects from the scan area that contribute to distortion is necessary since MRI, CT, and PET/CT images are susceptible to artifacts and noise; make sure that the established rules for positioning the patient are followed for better visualization. The patient should feel comfortably motionless for a long time.

In addition, the voxel size and signal intensity have a great influence on radiomic signs, therefore, ensuring the standardization of protocols is important when setting up the scan [32, 33]. The effect of reconstruction filters on image quality and signal intensity should also be taken into account, namely a filter should be chosen that does not lose the useful signal and ensure high reproducibility of radiomic signs when performing PET/CT and CT [34].

The image matrix is scaled and reduced to an isotropic (square) form as part of image preprocessing [35]. Signal intensity normalization to one scale is also recommended, especially for MRI. For this purpose, statistical methods are used, for example ANTsR and WhiteStripe [36]. Signal intensity inhomogeneity phenomena may be encountered when performing MRI, which are caused not by biological properties of tissues, but by technical factors. In such cases, correction for this heterogeneity is required, which should be included in the quality control system of performed procedures.

Post-processing control

Tools and algorithms with proven accuracy of their work should be used for post-processing process [36]. For example, for the subsequent correct analysis of radiomic signs, it is important to use high-quality tools at the segmentation stage. Previously semi-automatic algorithms with manual segmentation correction were used, but now more and more algorithms based on artificial intelligence technologies [37] appear, which must undergo appropriate tests [38].

Monitoring of isolated radiomic signs and validation of imaging biomarkers

Principles of standardization and quality control of studies and procedures for pre- and post-processing of images are required to ensure the quality (bias and variability) of

radiomic signs, as well as reliability of imaging biomarkers [39].

At this stage, quality control tools are used, such as phantoms, which enable the assessment of bias and reproducibility of distinguished signs. Phantoms can be both digital and physical, made using substances of specified parameters [40, 41]. For example, for multicenter studies of breast cancer, an appropriate phantom is used, which enables the evaluation of study reproducibility and accuracy [42].

The phantom is scanned repeatedly under different conditions, after which the variability of measurements is calculated and compared with the threshold value that the European Medicines Agency recommends, which is no more than 15% to analyze the effect of the scanning parameters on variability and methodology of study and post-processing performance [39].

Accuracy is assessed in the process of studies on phantoms or on tissue samples and corresponds to the relative error when the true value of signs (ground truth) and measured ones are compared. Setting the threshold value for successful completion of assessment at the level of 15% is recommended in the process of imaging biomarker validation [39].

This field of radiomics is under development, which may become an effective method for diagnosing tumors and predicting process analysis in the near future. We believe that the number of studies in this field will increase with the introduction of artificial intelligence algorithms to create relationships between the selected signs and clinical data. However, without the implementation of the described quality control approaches at all stages, obtaining a solid evidence is impossible, i.e., data reproducible on other populations, other equipment with a bias indicators within the established limit. Phantoms were previously developed for monitoring quantitative modes of MRI (with diffusion indicators) and CT (with indicators of bone mineral density) at the Center for Diagnostics and Telemedicine. From our point of view, interaction with technical specialists (medical physicists, engineers) and medical personnel is necessary to develop phantoms with specified measurement accuracy in planning a study of radiomic signs and further obtaining imaging biomarkers in this work.

ROLE OF DEVELOPMENT OF VISUALIZATION BIOMARKERS

In recent years, efforts were made to improve approaches to standardization of radiomic signs by defining standard data collection protocols. Particular efforts for this were made by the QIN created by the National Cancer Institute (NCI), as well as RSNA, the Quantitative Imaging Biomarkers Alliance (QIBA) and others. In 2010, NCI launched an initiative of the Cancer Institute Centers for Quantitative Image Excellence, and the creation of a National Clinical Trials Network has become a key focus of this effort [43]. Centers for

quantitative image improvement create PET/CT, CT, and MR phantoms, as well as protocols for standardization, and QIBA provides consensus decisions on the accuracy of quantitative biomarker imaging measurements and requirements/procedures necessary to achieve this level of accuracy [29, 35, 36, 44, 45].

Since the term “radiomics” appeared in the scientific literature, hundreds of published radiomics studies aimed to improve the quality of diagnostics, treatment, and prognosis of cancer. An increasing number of works demonstrate the value of imaging biomarkers as an additional tool for clinical decision-making and role of machine learning algorithms in it [46].

One of the earliest applications of the radiomics-based method is the successful detection of tumors in the imaging of lung and breast cancers.

Breast cancer is a pathology that most often occurs in women worldwide. Accurate diagnosis and early prediction of treatment response are key aspects in clinical practice since it is a well-known heterogeneous disease [47]. Several studies used radiomics to predict breast cancer subtype or ER, PR, Ki67, and HER2 status on mammography [48], PET/CT [49, 50], and MRI [51, 52]. In addition to characterizing breast cancer, radiomics may also provide a non-invasive approach to predict metastases in the sentinel lymph nodes [53].

Most radiological research on breast cancer focuses on therapy response evaluation. H.M. Chan et al. [54] developed an automated method using MRI to predict the absence or insufficient response to treatment in patients with early breast cancer. Most other studies attempted to obtain a pathologic complete response (pCR) biomarker with neoadjuvant chemotherapy, a hot topic of discussion in studies on breast cancer. Thus, N.M. Braman et al. [55] revealed that intra- and peri-tumor characteristics found on dynamic contrast-enhanced MRI can predict pCR prior to treatment. Other studies also showed that T1WI, T2WI, and DWI can aid in pCR detection [56, 57].

Radiological studies focused on the prognosis of breast cancer are performed more and more frequently. For example, H. Park et al. [58] developed an algorithm combining MRI imaging biomarkers and clinical information to individually assess the survival ability of patients with breast cancer.

Lung cancer is the most dangerous type of cancer, and its prevalence also continues to increase worldwide. Lung cancer screening is one of the most important diagnostic applications of radiomics. N. Nasrullah et al. [59] proposed a deep learning model based on chest CT studies from the LIDC-IDRI dataset and achieved good results in detecting malignant lung nodules with a sensitivity of 94% and specificity of 91%. B.W. Carter et al. [60] conducted a screening study of patients diagnosed with lung cancer in the National Lung Screening Trial dataset using low-dose CT. They were able to obtain predictive accuracy of 80% and 79% for nodules that develop into malignant neoplasms in one or two years, respectively.

Radiomics enables the determination at the preoperative stage in staging lung cancer by tumor nodules metastasis (TNM) [61, 62], which is important for making a decision about surgical intervention. In addition, the technique can be used to detect specific genetic mutations in lung cancer, such as the status for the *Estimated glomerular filtration rate* gene [63] which can help medical specialists choose the optimal therapeutic approach. X. Fave et al. used delta-radiomic characteristics to predict outcomes in patients with stage III non-small cell lung cancer during radiation therapy [64]. Their results suggest that changes in radiomic characteristics due to radiation therapy will be indicative of tumor response. T.P. Coroller et al. [65] established that radiomic signs of CT before treatment can predict a pathological response after neoadjuvant chemoradiation therapy in patients with advanced non-small cell lung cancer.

In recent years, radiomics are increasingly used for diagnostics, treatment response prediction, and long-term outcomes of tumors of the nervous system [26, 66, 67], head and neck [68, 69], gastrointestinal tract [70, 71], prostate cancer [72, 73], and some other forms of oncological diseases [74].

CONCLUSION

Early detection and identification of tumors, their heterogeneity, and phenotypic signs can be invaluable in patient stratification, subsequent treatment options determination, and effects prediction. Radiomic analysis of diagnostic studies provides information necessary for this, but only under conditions of high-quality collected and processed data. All of these processes need to be standardized and optimized using a variety of quality control methods, and at each stage, from image acquisition to validation of imaging biomarkers. In addition, clinical information must be taken into account, based on which the search for clinical correlations is performed to establish the prognostic value of biomarkers. Only the qualitative fulfillment of all these criteria can make the biomarker imaging tool really useful for doctors and necessary for patients.

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AUTHORS' INFO

*** Anna N. Khoruzhaya, MD;**

address: 28-1 Srednyaya Kalitnikovskaya str., 109029 Moscow, Russia; ORCID: <https://orcid.com/0000-0003-4857-5404>; eLibrary SPIN: 7948-6427; e-mail: a.khoruzhaya@npcmr.ru

Ekaterina S. Akhmad;

ORCID: <https://orcid.com/0000-0002-8235-9361>; eLibrary SPIN: 5891-4384

Dmitry S. Semenov;

ORCID: <https://orcid.com/0000-0002-4293-2514>; eLibrary SPIN: 2278-7290

ОБ АВТОРАХ

*** Хоружая Анна Николаевна;**

адрес: Россия, 109029, Москва, Средняя Калитниковская ул., д. 28, стр. 1; ORCID: <https://orcid.com/0000-0003-4857-5404>; eLibrary SPIN: 7948-6427; e-mail: a.khoruzhaya@npcmr.ru

Ахмад Екатерина Сергеевна;

ORCID: <https://orcid.com/0000-0002-8235-9361>; eLibrary SPIN: 5891-4384

Семенов Дмитрий Сергеевич;

ORCID: <https://orcid.com/0000-0002-4293-2514>; eLibrary SPIN: 2278-7290

* Corresponding author / Автор, ответственный за переписку