Cancer Management and Research

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Application of Radiomics for Personalized Treatment of Cancer Patients

This article was published in the following Dove Press journal:
Cancer Management and Research

Yiming Meng[1]
Jing Sun[1]
Na Qu[2]
Guirong Zhang[1]
Tao Yu[3]
Haozhe Piao[1,4]

[1]Central Laboratory, Cancer Hospital of China Medical University, Liaoning Province Cancer Hospital, Shenyang 110042, People's Republic of China; [2]Department of Gynecology, Cancer Hospital of China Medical University, Liaoning Province Cancer Hospital, Shenyang 110042, People's Republic of China; [3]Department of Medical Image, Cancer Hospital of China Medical University, Liaoning Province Cancer Hospital, Shenyang 110042, People's Republic of China; [4]Department of Neurosurgery, Cancer Hospital of China Medical University, Liaoning Province Cancer Hospital, Shenyang 110042, People's Republic of China

Abstract: Radiomics is a novel concept that relies on obtaining image data from examinations such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET). With the appropriate algorithm, the extracted results have broad applicability and potential for a massive positive impact in radiology. For example, clinicians can verify treatment efficiency, predict the location of tumor metastasis, correlate results with a histopathological examination, or more accurately define the type of cancer. Combining radiomics with other testing techniques allows every patient to have a personalized treatment plan that is essential for advanced examination and treatment. This article explains the process of radiomics, including data collection mechanisms, combined use with genomics, and artificial intelligence and immunology techniques, which may solve many of the challenges faced by doctors in diagnosing and treating their patients.

Keywords: radiology, personalized therapy, workflow, genomics, artificial intelligence, immunology

Introduction

Clinical tumor diagnosis technology assists health care workers in making medical decisions. Conventionally, cancer diagnosis and classification is based on histological examination of biopsy specimens, but these classical methods are bound for disruption by new, non-invasive technologies. New techniques, such as radiomics, look at individual differences that exist in cancer cells in order to determine a personalized, highly targeted treatment course, solutions that classical methods cannot provide.[1,2] In response to deficiencies in tissue testing, non-invasive medical imaging, such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) are used to assess tumor locations and metastases.[3] In addition, imaging provides valuable information for personalized medicine. When combined with traditional histology and new high-throughput platforms, non-invasive imaging can diagnose tumors earlier and more accurately, allowing tumor staging and prognosis at a level that truly achieves the concept of precision medicine.[4] Precision medicine is a component of personalized treatments intended to design patient-tailored therapies that optimize the genotype and phenotypic characteristics of an individual (for example, using patients' genes and their transcripts, proteins, and metabolites). Research in precision medicine involves systems biology methods that integrate mathematical modeling, biogenomics, transcriptomics, proteomics, and metabolomics. In addition, precision medicine necessarily considers not only the relatively static genetic code of an individual but also

Correspondence: Haozhe Piao
Department of Neurosurgery, Cancer Hospital of China Medical University, Liaoning Province Cancer Hospital, No. 44, Xiaoheyan Road, Dadong District, Shenyang 110042, People's Republic of China
Tel +86-180-413-94586
Fax +86-24-31916472
Email haozhepiaolnzlyy@sina.com

Tao Yu
Department of Medical Image, Cancer Hospital of China Medical University, Liaoning Province Cancer Hospital, No. 44, Xiaoheyan Road, Dadong District, Shenyang 110042, People's Republic of China
Email taoyulnszlyy@sina.com

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/CMAR.S232473

the dynamic and heterogeneous genetic code of cancer.[5,6] Therefore, precision medicine relies on the discovery of identifiable treatment targets and monitoring modifications, and also on reliable, non-invasive methods to identify changes in these targets over time.[7]

Although medical imaging techniques can be used to assess tumor heterogeneity, imaging features are primarily characterized qualitatively by radiologists or nuclear medicine physicians. This visual assessment process is influenced by internal tumor conditions, lymph node inflammatory hyperplasia, and the subjective factors of the observer. Thus, improving the objectivity and reproducibility of imaging techniques and quantifying the internal conditions of the tumor more comprehensively will reveal imaging features such as potential biological changes of the tumor,[8,9] which is driving the growth of the radiomics field. Radiomics uses high-throughput technology to extract advanced quantitative analyses describing the tumor phenotype objectively and quantitatively. Radiomics algorithms, thus, find clinically essential information in medical images that are invisible to a human observer—and tumor characteristics are the most valuable diagnostic information for personalized medicine.[10,11]

The term 'radiomics' originated in 2012 and was first introduced as a scientific discipline in advanced medical imaging analysis. In addition to the micro-heterogeneity associated with cell imaging and molecular markers of tumors based on medical imaging, there are recent categorizations and analyses of tumors and phenotypes,[12,13] localized regional modeling,[14] and applications such as prediction of future results.[15] Other, more quantitative, imaging models for specific tumor sites include head and neck,[16,17] lung,[18] breast,[19] liver,[20] cervix,[21] prostate,[22] limbs (sarcoma),[23] and the brain.[24] In the past five years, the field of radiology has garnered much more attention from experts in other fields, and the number of medical imaging publications has grown exponentially. Thus, knowledge about the scope and application of radiomics, within many sub-disciplines of radiology, is expanding rapidly and broadly.[25] In the next few years, international cooperation, well-designed clinical trials, and joint testing will be the most beneficial research that promotes the clinical application of advanced radiology techniques.[26] This review provides a summary of the latest research in radiological spectroscopy in the joint diagnosis of cancer, improves the awareness of radiology and promotes its clinical application.

Radiology Workflow

The process of radiomics is (1) acquisition of image data, (2) calibration of tumor regions, (3) segmentation of tumor regions, (4) extraction and quantification of features, (5) image database establishment, and (6) classification and prediction. Traditional radiological tests are used to distinguish tumor types and predict a patient's survival or tumor recurrence. Proper data selection is critical for creating an effective model, which requires a massive amount of data collection and aggregation to eliminate the effects of individual differences. In addition, the quality of the data depends on the imaging characteristics of the imaging instrument, reconstruction methods, and dynamic artifacts. Therefore, image acquisition and standardized operational procedures facilitate the generation of high-quality data sets.[27,28]

After image acquisition and volume reconstruction, a region of interest (ROI) can be defined. In the constructed 3D image of the tumor, the tumor image is observed layer-by-layer; this workload can be reduced with semi-automatic segmentation that also eliminates human error. Image segmentation, operational flow, slice spacing, reconstruction methods, time points, and respiratory motion all affect image reproducibility.[29] Since the extracted features' value mainly depends on image reconstruction and preprocessing methods, proper use of filtering techniques, intensity separation methods, and voxel resampling play a crucial role in the operability of radiomics.[30,31] Next, extracted features are aggregated with clinical and pathological results to construct a classification, prediction, or prognostic model, together forming a big data set. Once this comprehensive big data set is available, it is possible to build a variety of different machine learning models (such as neural networks, decision trees, support vector regression, and multivariate techniques), which affect the modeling process and the prediction model. Prediction is based on the feature set of radiation characteristics used in the construction, which can be used to predict the performance characteristics for internal validation or evaluate an external model.[32] An internal validation model (for assessing and mitigating performance) is necessary. Data is used to train the model, which may be performed by methods such as analysis or verification of a baseline intersection. An external validation set (using separate external data) is used to verify the accuracy of the prediction model or evaluate a universal prediction model.[33,34]

The goal of many radiology-focused guidelines is to provide details on model development and validation to provide better repeatability and critical assessment of predictive models. In future research, attention should be given to calibrating the radiomics quality scoring (RQS) and transparent reporting of a multivariable prediction model for an individual prognosis or diagnosis (TRIPOD) model,[35] to determine whether the operational procedures are clinically suitable, and to promote the growing maturity of radiomics.

Combining Radiomics with Genomics

For tumors, the goal of precision medicine is to link the tumor phenotype to a clinical endpoint in order to improve clinical decision making. Imaging through radiomics and genomics will play an essential role in precision medicine.[36] In 2003, the European Society for Radiotherapy and Oncology (ESTRO) first proposed the concept of radiogenomics (also known as imaging genomics), which aims to establish a correlation between gene expression profile data and imaging features.[37] In 2007, in the journal Nature Biotechnology, Israeli scholar Segal et al[38] proposed a three-step strategy to establish a correlation map between image features and gene expression profiles. That study used a three-stage contrast-enhanced CT scan to obtain 28 image features and the gene expression profile of patients with primary hepatocellular carcinoma, illustrating the three-step strategy. That three-step strategy has become the standard for radiogenomics research.

Radiomics enhances radiogenomics by extracting enormous amounts of quantitative data from digital images, then documenting these with clinical and patient data into a shared database that also includes genetic and radiomic data. Radiogenomics provides voxel-by-voxel genetic information or provides primary tumor information, in the case of metastatic disease, to guide clinical treatment. In addition, radiogenomics quantifies lesion characteristics and better differentiates between benign and malignant tumors to stratify patients based on disease risk, for more accurate imaging and screening of tumors.[39,40]

In 2015, Mu Zhou and others collected preoperative CT data, and postoperative tumor specimens from 113 patients with non-small cell lung cancer (NSCLC) diagnosed between April 2008 and September 2014 as subjects. Radiographic features included nodular shape, margin, texture, tumor environment, and overall lung characteristics. Changes in genetic information in the corresponding tumor tissue were detected by RNA sequencing. That research found that 10 meta-genes defined multiple molecular pathways, including the epidermal growth factor (EGF) pathway, and also found meta-genes associated with frosted glass opaque shadows, irregular nodules, and undefined knots on the margins.[41] Further, recent studies have found that colorectal cancer (CRC) is characterized by significant intratumorally genetic heterogeneity, which can be evaluated on medical images also. A high-throughput platform has been developed to obtain genomic and transcriptional group data to characterize cancer at the molecular level better. The current clinical application of genomic information comes from mutational data from the Kirsten rat sarcoma virus (KRAS), Neuroblastoma RAS viral oncogene homolog (NRAS) and RAF murine sarcoma viral oncogene homolog B (BRAF) genes, which are effectors of the MAPK (mitogen-activated protein kinase) pathway, as prognostic and specific biomarkers, including HER2 for targeted gene therapy. Bogdan and other scholars combined CT radiology, gene expression analysis, histopathological examination of primary CRC, and survival analysis to show that enhanced CT and gene expression can more effectively predict the prognosis of primary CRC, and it is also beneficial to develop treatment plans.[42] Experts such as Pascal O. Zinn used image segmentation technology, radiological feature extraction, feature normalization, and selection and predictive modeling to establish a combined analysis method for skull stripping and brain tissue standardization, allowing cross-platform and cross-institutional comparison. The study of radiomics also uncovered that the radiographic texture characteristics of glioma might be causally related to the expression of periostin (POSTN).[43] Because of a strong correspondence between radiology and the genome, Claudia Kesch and other scholars further demonstrated that radiomics technology, including multi-parameter magnetic resonance imaging (MRI), 68Ga-prostate-specific membrane antigen (PSMA)-PET/CT imaging combined with genetic testing can guide the diagnosis and distinguish between in situ and invasive prostate cancer.[44] Various studies have shown that combining radiomics with genetic testing provides not only more accurate test results but also provides more effective treatment plans.

Combining Radiomics with Artificial Intelligence

Artificial intelligence (AI) is a loosely-defined concept of the intelligence exhibited by machines, as opposed to the

natural intelligence exhibited by humans and other animals. However, in the context of medical imaging, we specifically define AI as a system that "correctly interprets external data and extracts information from these data, using it flexibly to achieve specific goals and tasks.[45]" AI systems are used for analysis, personal inspiration, or personified AI. In the twenty-first century, artificial intelligence technology benefits from improved theoretical understanding (such as in neural network mathematics), advances in computer functions (such as graphics processing units [GPU]), and high-end data processing platforms (such as cloud storage and computing), as well as the operability of the algorithm and the database itself. Concerning medical imaging, it is theoretically possible to perform many tasks, related to images, through AI techniques, including lesion detection, disease classification, diagnosis and staging, quantification, treatment planning, and assessment of response to treatment and prognosis.[46,47]

Recent studies found that radiomics combined with AI provide additional improvements, such as improved operational workflow, financial management, and quality. For example, AI (trained via machine learning) was applied to preoperative MRI studies to distinguish between low-level and high-level tumors using image texture features obtained using multi-mode MRI to achieve World Health Organization (WHO) tumor grading levels. Clinically relevant molecular subtypes of glial cells, such as the presence of isocitrate dehydrogenase (IDH) mutations, can be diagnosed by intensive learning by training machines, such as the convolutional neural network (CNN) method.[48] In addition to neurological tumors, there are applications in breast cancer. Since the 1980s, the five-year survival rate of breast cancer has been demonstratively improved. In addition to improving treatment methods, this also significantly relates to the reform in breast imaging screening. Breast cancer is a heterogeneous disease, and the presence of estrogen receptor (ER) is important for the response of specific treatments (such as tamoxifen) and prognosis (poor prognosis in ER-negative patients) and can define the etiology type. Triple-negative—ER-negative, progesterone receptor (PR)-negative, human epidermal growth factor receptor (HER2)-negative—breast cancer has a poor five-year survival rate. There are no typical signs of a breast cancer malignancy, which means interval or high-grade tumors might be misdiagnosed.[49] With the advancement of radiomics and computer analysis capabilities, the response of breast tumors to treatment has improved, from the perspective of detection and diagnosis.

Despite the success of AI in cancer imaging, some limitations and barriers must be overcome before extensive clinical use. With the continuous advancement of systems such as Picture Archiving and Communication Systems (PACS) and Medical Digital Imaging and Communications (DICOM), the needs for imaging are shifting to access and retrieval.[50,51] However, these data are rarely set-up ahead of time in terms of labeling, annotation, segmentation, quality assurance, or adaptability, and thus, even advanced AI technology may fail. However, as the power and potential of AI are increasingly recognized, there are many ways in which AI can be transformed into conventional clinical practice. For imaging analysis, if AI is to replace some parts of a clinician's work, the accuracy of the diagnosis, and the ability to predict the disease must keep improving. Globally, the lack of imaging experts means clinical needs are not met worldwide. AI technology can reduce the cost and training of clinicians by providing a range of imaging diagnostic tools for uncommon diseases. In short, AI has an extensive range of applications in medical imaging. It is easy to see from early research that AI has made meaningful progress in adding intelligence to medical imaging equipment, standardization of data acquisition, and automation of data analysis. The combination of AI and radiomics will produce dramatic social and economic benefits, and rapidly improve the level of diagnosis and treatments by grassroots doctors, with the accumulation of more data and the continued maturity of the technology.[52–54]

Combining Radiomics with Tumor Biomarkers

The National Institutes of Health (NIH) defines biomarkers as "a major indicator that can be measured and used to assess changes in a normal biological process, pathogenic process, or treatment intervention." Valuable tumor markers must guide clinical decision making to improve the patient's disease status.[52,55] The combination of radiomic and biomarkers is a multi-step development process. Moreover, this combination will undoubtedly improve the accuracy and timeliness of cancer diagnosis, reduce trauma to patients, and reduce healthcare costs.

Professor Wang Dengbin and his team in China retrospectively studied 177 patients with rectal adenocarcinoma (confirmed by histopathology) and collected 385 radiomic groups. Features of the study were establishing a clinical-radiomics combinatorial model, validating predictive

performance through receiver operating characteristic curve (ROC) analysis, implementing clinical routines for nomogram and decision curve analysis, and predictive radioscopy combined with clinical detection of tumor markers in prediction the value of synchronous distant metastasis (SDM) in rectal cancer. The experimental results demonstrated that clinical radiology combined with CEA and CA199 molecular models could be used as non-invasive biomarkers to identify high-risk patients with SDM, which helps to customize treatment strategies.[56]

Immunohistochemistry (IHC) is a well-established technique that assists pathologists in improving the accuracy and precision of diagnosis in the field of surgical pathology. IHC has moved beyond diagnostic applications in laboratory medicine and is now used to discover prognoses and predict biomarkers, which may lead to the development of more valuable cancer-targeted treatment strategies in the next era of personalized medicine.[57,58] In parallel with the deepening of imaging research, new analytical methods for the discovery of image-based biomarkers are making progress. Because of the need to associate image-based features with IHC markers, IHC has also become an essential part of radiology. Valuable tools and the combination of these types of biomarkers increase the depth of exploration of tumor biology to provide a variety of ways to guide clinical oncology.[59]

Clinical practice in radiology and pathology requires expertise and years of training to visually assess and interpret abnormal phenotypic features in medical images and tissue sections and then generate diagnostics that guide disease management and treatment. In prostate cancer IHC the most widely used markers are prostate-specific antigen (PSA), prostate-specific acid phosphatase (PSAP), Prostate-specific membrane antigen (PSMA), and p63; all are commonly used as a part of prostate radioimaging.[60] Despite the initial lack of correlation, the study also aimed to combine serum and urine biomarkers with diffusion-weighted imaging (DWI)-MRI to predict prostate cancer with vascular IHC markers and assess microvessel density in large prospective cohorts. In the future, the correlation between integrated radiology and IHC expression will provide clinicians with more diagnostic information and evidence to predict clinical outcomes and formulate a treatment response, which should significantly improve the quality and efficiency of medical services.

Combining Radiomics with Immunological Detection

Tumor immunotherapy has significantly improved the treatment for cancers such as melanoma, lymphoma, and lung cancer, but unfortunately, only 20–50% of patients with advanced solid tumors respond to treatment.[61,62] Therefore, there is an urgent need to develop a test that can determine the likely efficacy of immunotherapy. Numerous studies have indicated that the effectiveness of immunotherapy is related to the number and function of immune cells in tumors and peritumoral invasiveness. In immunotherapy, three different reaction states are produced: the immune response phase, the immune exclusion phase, and the immune cell deficiency phase. Tumors in the immune response phase are characterized by dense functional CD8 cell infiltration, increased expression of interferon-gamma, and cell checkpoint markers (e.g., PD-L1), which tend to respond to immunotherapy. In the immune rejection phase, several biological signals are generated in the tumor, including the signal of transforming growth factor-β, activation of myeloid-derived suppressor cells, and angiogenic signals, suggesting that T cell infiltration is inhibited.[63,64] The immunodeficiency phase is characterized by a low infiltration of CD8 cells.

Radiomics can assess the immune infiltration of tumors and thus become a novel predictor of the efficacy of immunotherapy. Roger Sun and colleagues reported CD8 cell expression profiles based on eight-feature radiology, which were developed using CT images and RNA sequencing data from 135 patients enrolled in the MOSCATO trial. The consistency of radiology histological features with gene expression was confirmed by comparison with the genetic markers of CD8 cells. The study used data from 119 patients from the Cancer Genome Atlas dataset and 100 patients from their registry that stratified tumors into high-CD8 cell and low-CD8 cell infiltration, to make this comparison. While radioimmunological features have been shown to correlate with clinical outcomes in independent cohort patients who have been treated with anti-PD-1 or PD-L1 immunotherapy, to the best of our knowledge, this is one of the first studies to correlate pathology with clinical outcomes using radioimmuno-based biomarkers. Therefore, this study provides a potential role for stimulation analysis of radiomics for personalized immunotherapy.[65] Chinese imaging experts Tian Jie and Professor Yu Ming recently developed a radiological model based on gadolinium ethoxybenzyl diethylenetriamine (Gd-EOB-DTPA) enhanced MRI, combined with intra-tumor and peri-tumor radiographic features.

The model, which uses clinical data and a select combination of radiographic features, first attempted to provide comprehensive radiomics using a combination of novel intra-tumor and peri-tumor radiology to suggest tumor-infiltrating lymphocytes (TIL) density better.[66] Through this research, it was found that the combination of radiomic results and immunological characteristics in the analysis of tumor prognosis or prediction could predict results more accurately, which is also a goal of radiomics.

Conclusion

Radiomics is the product of the era of big data. Sufficient feature data and database construction are the premises of imaging radiomics research. At present, many radiomic studies have small sample sizes. Small data sets generated by insufficient sample sizes reduce the accuracy of a model's prediction and increase the risk of overfitting.[67–69] Therefore, many problems and challenges in radiomics must be addressed. Firstly, because of the semi-automatic or manual delineation of ROI, there are subjective differences. The repeatability of the extracted features needs further observation, and the analysis results from the texture parameters extracted by 2D and 3D ROI are different, which leads to poor data repeatability. Secondly, each study has different choices and different approaches to feature extraction and quantification and modeling. Most studies have found the appropriate feature extraction and modeling method through trial and error. However, the human bias and randomness of this method are significant. The statistics and data for most of the radiomic studies have not been verified by an independent cohort study, so the patient population is not universal. Finally, the degree of standardization is not high. Since most studies are retrospective studies, the methods for acquiring and reconstructing images and the standards for radiomics post-processing have not been standardized. The images (CT, MRI, PET-CT) of each study were of different quality, and the radiomic processing software used was different, and the results obtained by different scanners were also different.

With the advocacy of precision therapy, radiomics provide an innovative approach to personalized medicine with low cost, non-invasiveness, and avoidance of unnecessary treatment and toxicity risks. In the future, a large amount of data will be available for radiomics to predict tumor stage, distinguish between healthy tissue and pathological tissue, detect genetic characteristics, and predict response to treatment, patient survival, and drug side effects. Despite the great promise of radiomics, these radiological features must be combined with other relevant sources of information (e.g., biology, genomics, and immunology) to improve the prognosis and predictive value of personalized medicine treatments.

Acknowledgment

This research work was supported by the Natural Science Foundation (20180550488 to Yiming Meng) of Liaoning Province, Excellent Talent Fund of Liaoning Province Cancer Hospital of Yiming Meng, and Millions of Talents Project Leading Talent (XLYC1805001 to Tao Yu).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Wenya LB, Ahmed H, Matthew BS, et al. Artificial intelligence in cancer imaging: clinical challenges and applications. *CA Cancer J Clin*. 2019;69(2):127–157. doi:10.3322/caac.21552
2. Castro-Giner F, Gkountela S, Donato C, et al. Cancer diagnosis using a liquid biopsy: challenges and expectations. *Diagnostics*. 2018;8(2):31. doi:10.3390/diagnostics8020031
3. European Society of Radiology (ESR). Medical imaging in personalised medicine: a white paper of the research committee of the European Society of Radiology (ESR). *Insights Imaging*. 2015;6(2):141–155. doi:10.1007/s13244-015-0394-0
4. Lu M, Zhan X. The crucial role of multiomic approach in cancer research and clinically relevant outcomes. *EPMA J*. 2018;9(1):77–102. doi:10.1007/s13167-018-0128-8
5. Wang L. Pharmacogenomics: a systems approach. *Wiley Interdiscip Rev Syst Biol Med*. 2010;2(1):3–22. doi:10.1002/wsbm.v2:1
6. Zhang L, Hong H. Genomic discoveries and personalized medicine in neurological diseases. *Pharmaceutics*. 2015;7(4):542–553. doi:10.3390/pharmaceutics7040542
7. Maggi E, Patterson NE, Montagna C. Technological advances in precision medicine and drug development. *Expert Rev Precis Med Drug Dev*. 2016;1(3):331–343. doi:10.1080/23808993.2016.1176527
8. Ottlakan A, Borda B, Morvay Z, et al. The effect of diagnostic imaging on surgical treatment planning in diseases of the thymus. *Contrast Media Mol Imaging*. 2017;2017:9307292. doi:10.1155/2017/9307292
9. Pysz MA, Gambhir SS, Willmann JK. Molecular imaging: current status and emerging strategies. *Clin Radiol*. 2010;65(7):500–516. doi:10.1016/j.crad.2010.03.011
10. Bagheri MH, Ahlman MA, Lindenberg L, et al. Advances in medical imaging for the diagnosis and management of common genitourinary cancers. *Urol Oncol*. 2017;35(7):473–491. doi:10.1016/j.urolonc.2017.04.014
11. Morin O, Vallieres M, Jochems A, et al. A deep look into the future of quantitative imaging in oncology: a statement of working principles and proposal for change. *Int J Radiat Oncol Biol Phys*. 2018;102(4):1074–1082. doi:10.1016/j.ijrobp.2018.08.032
12. Aerts HJWL, Velazquez ER, Leijenaar RTH, et al. Decoding tumor phenotype by noninvasive imaging using a quantitative radiomics approach. *Nat Commun*. 2014;5:4006. doi:10.1038/ncomms5006
13. Gillies RJ, Anderson AR, Gatenby RA, et al. The biology underlying molecular imaging in oncology: from genome to anatome and back again. *Clin Radiol*. 2010;65:517–521. doi:10.1016/j.crad.2010.04.005
14. Vallières M, Kay-Rivest E, Perrin LJ, et al. Radiomics strategies for risk assessment of tumor failure in head-and-neck cancer. *Sci Rep*. 2017;7:10117. doi:10.1038/s41598-017-10371-5

15. Parmar C, Leijenaar RTH, Grossmann P, et al. Radiomic feature clusters and prognostic signatures specific for lung and head & neck cancer. *Sci Rep*. 2015;5:11044. doi:10.1038/srep11044
16. Elhalawani H, Kanwar A, Mohamed ASR, et al. Investigation of radiomic signatures for local recurrence using primary tumor texture analysis in oropharyngeal head and neck cancer patients. *Sci Rep*. 2018;8:1524.
17. Jethanandani A, Lin TA, Volpe S, et al. Exploring applications of radiomics in magnetic resonance imaging of head and neck cancer: a systematic review. *Front Oncol*. 2018;8:131. doi:10.3389/fonc.2018.00131
18. Tseng HH, Luo Y, Cui S, et al. Deep reinforcement learning for automated radiation adaptation in lung cancer. *Med Phys*. 2017;44:6690–6705. doi:10.1002/mp.12625
19. Dong Y, Feng Q, Yang W, et al. Preoperative prediction of sentinel lymph node metastasis in breast cancer based on radiomics of t2-weighted fat-suppression and diffusion-weighted mri. *Eur Radiol*. 2018;28:582–591. doi:10.1007/s00330-017-5005-7
20. Cozzi L, Dinapoli N, Fogliata A, et al. Radiomics based analysis to predict local control and survival in hepatocellular carcinoma patients treated with volumetric modulated arc therapy. *BMC Cancer*. 2017;17:829. doi:10.1186/s12885-017-3847-7
21. Lucia F, Visvikis D, Desseroit MC, et al. Prediction of outcome using pretreatment (18)f-fdg pet/ct and mri radiomics in locally advanced cervical cancer treated with chemoradiotherapy. *Eur J Nucl Med Mol Imaging*. 2018;45:768–786. doi:10.1007/s00259-017-3898-7
22. Gnep K, Fargeas A, Gutierrez-Carvajal RE, et al. Haralick textural features on t2-weighted mri are associated with biochemical recurrence following radiotherapy for peripheral zone prostate cancer. *J Magn Reson Imaging*. 2017;45:103–117. doi:10.1002/jmri.25335
23. Vallieres M, Laberge S, Diamant A, et al. Enhancement of multimodality texture-based prediction models via optimization of pet and mr image acquisition protocols: A proof of concept. *Phys Med Biol*. 2017;62:8536–8565. doi:10.1088/1361-6560/aa8a49
24. Chang K, Bai HX, Zhou H, et al. Residual convolutional neural network for the determination of idh status in low- and high-grade gliomas from mr imaging. *Clin Cancer Res*. 2018;24:1073–1081. doi:10.1158/1078-0432.CCR-17-2236
25. Lambin P, Leijenaar RTH, Deist TM, et al. Radiomics: the bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol*. 2017;14:749–762. doi:10.1038/nrclinonc.2017.141
26. European Society of Radiology (ESR); European Federation of Radiographer Societies (EFRS). Patient safety in medical imaging: a joint paper of the European Society of Radiology (ESR) and the European Federation of Radiographer Societies (EFRS). *Insights Imaging*. 2019;10(1):45. doi:10.1186/s13244-019-0721-y
27. Dutta J, Ahn S, Li Q. Quantitative statistical methods for image quality assessment. *Theranostics*. 2013;3(10):741–756. doi:10.7150/thno.6815
28. Chen JE, Glover GH. Functional magnetic resonance imaging methods. *Neuropsychol Rev*. 2015;25(3):289–313.
29. Jun Y, Eo T, Kim T, et al. Deep-learned 3D black-blood imaging using automatic labelling technique and 3D convolutional neural networks for detecting metastatic brain tumors. *Sci Rep*. 2018;8(1):9450. doi:10.1038/s41598-018-27742-1
30. Madabhushi A, Udupa JK. New methods of MRI image intensity standardization via generalized scale. *Med Phys*. 2006;33:3426–3434. doi:10.1118/1.2335487
31. Tangaro S, Amoroso N, Brescia M, et al. Feature selection based on machine learning in MRIs for hippocampal segmentation. *Comput Math Methods Med*. 2015;2015:814104. doi:10.1155/2015/814104
32. Deo RC. Machine learning in medicine. *Circulation*. 2015;132(20):1920–1930. doi:10.1161/CIRCULATIONAHA.115.001593
33. Mahobia NK, Patel RD, Sheikh NW, et al. Validation method used in quantitative structure activity relationship. *Der Pharma Chem*. 2010;2(5):260–271.
34. Lazzarini N, Runhaar J, Bay-Jensen AC, et al. A machine learning approach for the identification of new biomarkers for knee osteoarthritis development in overweight and obese women. *Osteoarthritis Cartilage*. 2017;25(12):2014–2021. doi:10.1016/j.joca.2017.09.001
35. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *Ann Intern Med*. 2015;162:55–63. doi:10.7326/M14-0697
36. Ghasemi M, Nabipour I, Omrani A, et al. Precision medicine and molecular imaging: new targeted approaches toward cancer therapeutic and diagnosis. *Am J Nucl Med Mol Imaging*. 2016;6(6):310–327.
37. Rutman AM, Kuo MD. Radiogenomics: creating a link between molecular diagnostics and diagnostic imaging. *Eur J Radiol*. 2009;70(2):232–241. doi:10.1016/j.ejrad.2009.01.050
38. Segal E, Sirlin CB, Ooi C, et al. Decoding global gene expression programs in liver cancer by noninvasive imaging. *Nat Biotechnol*. 2007;25(6):675–680. doi:10.1038/nbt1306
39. Sala E, Mema E, Himoto Y, et al. Unravelling tumour heterogeneity using next-generation imaging: radiomics, radiogenomics, and habitat imaging. *Clin Radiol*. 2017;72(1):3–10. doi:10.1016/j.crad.2016.09.013
40. Liu Z, Wang S, Dong D, et al. The applications of radiomics in precision diagnosis and treatment of oncology: opportunities and challenges. *Theranostics*. 2019;9(5):1303–1322. doi:10.7150/thno.30309
41. Zhou M, Leung A, Echegaray S, et al. Non-small cell lung cancer radiogenomics map identifies relationships between molecular and imaging phenotypes with prognostic implications. *Radiology*. 2018;286(1):307–315. doi:10.1148/radiol.2017161845
42. Badic B, Hatt M, Durand S, et al. Radiogenomics-based cancer prognosis in colorectal cancer. *Sci Rep*. 2019;9(1):9743. doi:10.1038/s41598-019-46286-6
43. Pascal ZO, Sanjay SK, Aikaterini K, et al. A coclinical radiogenomic validation study: conserved magnetic resonance radiomic appearance of periostin-expressing glioblastoma in patients and xenograft models. *Clin Cancer Res*. 2018;24:6288–6299. doi:10.1158/1078-0432.CCR-17-3420
44. Kesch C, Radtke JP, Wintsche A, et al. Correlation between genomic index lesions and mpMRI and 68Ga-PSMA-PET/CT imaging features in primary prostate cancer. *Sci Rep*. 2018;8(1):16708. doi:10.1038/s41598-018-35058-3
45. Visvikis D, Le Rest CC, Jaouen V, Hatt M. Artificial intelligence, machine (deep) learning and radio(geno)mics: definitions and nuclear medicine imaging applications. *Eur J Nucl Med Mol Imaging*. 2019;46:2630–2637. doi:10.1007/s00259-019-04373-w
46. Su C, Jiang J, Zhang S, et al. Radiomics based on multicontrast MRI can precisely differentiate among glioma subtypes and predict tumour-proliferative behaviour. *Eur Radiol*. 2019;29(4):1986–1996. doi:10.1007/s00330-018-5704-8
47. Arimura H, Soufi M, Kamezawa H, et al. Radiomics with artificial intelligence for precision medicine in radiation therapy. *J Radiat Res*. 2019;60(1):150–157. doi:10.1093/jrr/rry077
48. Emblem KE, Due-Tonnessen P, Hald JK, et al. Machine learning in preoperative glioma MRI: survival associations by perfusion-based support vector machine outperforms traditional MRI. *J Magn Reson Imaging*. 2014;40(1):47–54. doi:10.1002/jmri.24390
49. Kravchenko J, Akushevich I, Seewaldt VL, et al. Breast cancer as heterogeneous disease: contributing factors and carcinogenesis mechanisms. *Breast Cancer Res Treat*. 2011;128(2):483–493. doi:10.1007/s10549-011-1347-z
50. Drop B, Drop K. Problems with implementation of the Radiological Information System (RIS) and Picture Archiving and Communication System (PACS) in laboratories of diagnostic imaging. *Collegium Econ Anal Ann*. 2017;46:267–282.
51. Nitrosi A, Corazza A, Bertolini M, et al. Patient dose management solution directly integrated in the RIS: "gray detector" software. *J Digit Imaging*. 2014;27:786. doi:10.1007/s10278-014-9715-y

52. Castiglioni I, Gallivanone F, Soda P, et al. AI-based applications in hybrid imaging: how to build smart and truly multi-parametric decision models for radiomics. *Eur J Nucl Med Mol Imaging*. 2019;3:1–27. doi:10.1007/s00259-019-04414-4
53. Rudie J, Rauschecker MA, Nick BR, et al. Emerging applications of artificial intelligence in neuro-oncology. *Radiology*. 2019;290:181928. doi:10.1148/radiol.2018181928
54. Visvikis D, Le Rest CC, Jaouen V, et al. Artificial intelligence, machine (deep) learning and radio(geno)mics: definitions and nuclear medicine imaging applications. *Eur J Nucl Med Mol Imaging*. 2019:1–8. doi:10.1007/s00259-019-04373-w
55. Strimbu K, Tavel JA. What are biomarkers? *Curr Opin HIV AIDS*. 2010;5(6):463–466. doi:10.1097/COH.0b013e32833ed177
56. Liu H, Zhang C, Wang L, et al. MRI radiomics analysis for predicting preoperative synchronous distant metastasis in patients with rectal cancer. *Eur Radiol*. 2019;29:4418. doi:10.1007/s00330-018-5802-7
57. Duraiyan J, Govindarajan R, Kaliyappan K, Palanisamy M. Applications of immunohistochemistry. *J Pharm Bioallied Sci*. 2012;4(Suppl 2):S307–S309. doi:10.4103/0975-7406.100281
58. Shin D, Arthur G, Caldwell C, et al. A pathologist-in-the-loop IHC antibody test selection using the entropy-based probabilistic method. *J Pathol Inform*. 2012;3:1. doi:10.4103/2153-3539.93393
59. Prescott JW. Quantitative imaging biomarkers: the application of advanced image processing and analysis to clinical and preclinical decision making. *J Digit Imaging*. 2013;26(1):97–108. doi:10.1007/s10278-012-9465-7
60. Alvi E, Gupta R, Borok ZR, et al. Overview of established and emerging immunohistochemical biomarkers and their role in correlative studies in MRI. *J Magn Reson Imaging*. 2019. doi:10.1002/jmri.26763
61. Marshall HT, Djamgoz MBA. Immuno-oncology: emerging targets and combination therapies. *Front Oncol*. 2018;8:315. doi:10.3389/fonc.2018.00315
62. Villanueva N, Bazhenova L. New strategies in immunotherapy for lung cancer: beyond PD-1/PD-L1. *Ther Adv Respir Dis*. 2018;12:1753466618794133. doi:10.1177/1753466618794133
63. Wrobel P, Ahmed S. Current status of immunotherapy in metastatic colorectal cancer. *Int J Colorectal Dis*. 2018;34. doi:10.1007/s00384-018-3202-8
64. El Naqa I, Ten Haken RK. Can radiomics personalise immunotherapy? *Lancet Oncol*. 2018;19(9):1138–1139. doi:10.1016/S1470-2045(18)30429-7
65. Sun R, Limkin EJ, Vakalopoulou M, et al. A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study. *Lancet Oncol*. 2018;19(9):1180–1191. doi:10.1016/S1470-2045(18)30413-3
66. Chen S, Feng S, Wei J, et al. Pretreatment prediction of immunoscore in hepatocellular cancer: a radiomics-based clinical model based on Gd-EOB-DTPA-enhanced MRI imaging. *Eur Radiol*. 2019;29:4177. doi:10.1007/s00330-018-5986-x
67. Paulson SS, Scruth E. Legal and ethical concerns of big data: predictive analytics. *Clin Nurse Spec*. 2017;31(5):237–239. doi:10.1097/NUR.0000000000000315
68. Marcu LG, Boyd C, Bezak E. Current issues regarding artificial intelligence in cancer and health care. Implications for Medical Physicists and Biomedical Engineers. *Health Technol*. 2019;9:375.
69. Dissaux G, Visvikis D, Do-Ano R, et al. Pre-treatment F-FDG PET/CT radiomics predict local recurrence in patients treated with stereotactic radiotherapy for early-stage non-small cell lung cancer: a multicentric study. *J Nucl Med Technol*. 2019. doi:10.2967/jnumed.119.228106