SA–CME Information

GENOMICS AND RADIOMICS: TOOLS TO SEE THE UNSEEN TO PERSONALIZE RADIATION THERAPY

Description

Genomics and radiomics provide an opportunity to increase the precision of radiation delivery in selection of dose and spatial delivery. Further understanding of host and tumor differences with interrogative approaches may provide opportunity to precisely deliver radiotherapy beyond spatial and anatomic features to one guided by intrinsic tumor biology. This article addresses how tumor genomic blueprints can be exploited for radiation therapy; radiomics as a noninvasive means to assessing tumor biology; clinical applications regarding treatment response, treatment planning, and toxicity; and radiogenomics utility.

Learning Objectives

After completing this activity, participants will be able to:

1. Obtain working knowledge of the current state of genomic and radiomic efforts in radiation oncology.
2. Learn about the quality control factors needed in working with big data in radiomic and genomic analyses.

Authors

G. Daniel Grass, MD, PhD, *is an assistant member and* ***Matthew N. Mills, MD,*** *is a radiation oncology resident, Department of Radiation Oncology, Lee Moffitt Cancer Center and Research Institute, Tampa, FL.* ***Jacob G. Scott, MD, DPhil,*** *is an assistant professor, Department of Translational Hematology and Oncology Research, Cleveland Clinic, Cleveland, OH.* ***Steven A. Eschrich, PhD,*** *is a senior member, Biostatistics and Bioinformatics, H. Lee Moffitt Cancer Center and Research Institute.* ***Javier Torres-Roca, MD,*** *is a senior member, Department of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute.*

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Date of release and review: December 1, 2019
Expiration date: November 30, 2021
Estimated time for completion: 1 hour

Disclosures: No authors, faculty, or individuals at the Institute for Advanced Medical Education (IAME) or *Applied Radiation Oncology* who had control over the content of this program have relationships with commercial supporters.

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Commercial Support: None

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Genomics and Radiomics: Tools To See the Unseen To Personalize Radiation Therapy

G. Daniel Grass, MD, PhD; Matthew N. Mills, MD; Jacob G. Scott, MD, DPhil; Steven A. Eschrich, PhD; Javier Torres-Roca, MD

Radiation therapy is a pillar of oncologic care for various solid malignancies in the curative and palliative settings. Technologic advancements spanning over a century have now provided opportunities for radiation to be delivered to the target of interest with high accuracy and precision. In this regard, implementation of 3-dimensional (3D) conformal radiation therapy and intensity-modulated radiation therapy (IMRT) coupled with daily image guidance have enhanced the achievable therapeutic ratio over a variety of dosing and fractionation schemes.[1]

Similar to medical oncology, radiation delivery has been guided by the fine balance of normal tissue toxicity and sustainability of durable tumor control. It is by these historical observations in which radiation dose has been chosen across a spectrum of malignancies and, to this day, remains the current dosing scheme for many cancers. Although it is generally accepted that tumors of the same stage, anatomic location and histology vary in their responses to radiation therapy, our field delivers treatment under a premise of established "clinical tolerance guidelines" rather than robust, tumor-specific, dose-response profiles.

In the last several decades, substantial advancements have been made in understanding the molecular catalog, metabolic networks and influence of the microenvironment on growth, spread and treatment response of various tumor types, yet employing these data in clinical decision-making has yet to inform the practice of radiation oncology. Furthermore, high-throughput analyses of clinically employed imaging modalities in radiation delivery has provided further opportunity to noninvasively categorize intrinsic tumor features and stratify patient outcomes. Further understanding of host and tumor differences with these interrogative approaches may provide the opportunity to precisely deliver radiation therapy beyond spatial and anatomic features, to one guided by intrinsic tumor biology.

Dr. Grass *is an assistant member and* ***Dr. Mills*** *is a radiation oncology resident, Department of Radiation Oncology, Lee Moffitt Cancer Center and Research Institute, Tampa, FL.* ***Dr. Scott*** *is an assistant professor, Department of Translational Hematology and Oncology Research, Cleveland Clinic, Cleveland, OH.* ***Dr. Eschrich*** *is a senior member, Biostatistics and Bioinformatics, H. Lee Moffitt Cancer Center and Research Institute.* ***Dr. Torres-Roca*** *is a senior member, Department of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute.* *Disclosure: Drs. Scott, Torres-Roca and Eschrich report intellectual property (IP); Drs. Scott and Torres-Roca report IP regarding genomically adjusted radiation dose (GARD), and Drs. Eschrich and Torres-Roca report stock in Cvergenx. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.*

Interrogation of Tumor Genomic Blueprints and Exploitation for Radiation Therapy

A major focus of personalized oncology has been the molecular characterization of tumors to identify unique druggable targets and generate higher order tumor classification methods to translate into clinical care.[2] Numerous high-throughput "-omics" analyses, which encompass transcriptional, proteomic, methylation, metabolomic and sequencing data, have provided unprecedented insight into the underlying biology of various human tumors.[3] These efforts have been largely performed within The Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium (ICGC) programs, although several academic and commercial organizations now perform Clinical Laboratory Improvement Amendments (CLIA)-certified analyses of tumor tissue to complement these efforts.[4]

The beginnings of precision oncology began with prior laboratory work, which identified the first cancer-related gene mutation in *HRAS* several decades

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Table 1. Selected Studies Developing Gene Signatures That Infer Intrinsic Radiosensitivity

Cancer Type	Number of Genes in Signature	Training Cohort(s)	Validation Cohort(s)	Reference(s)
Breast	34	343 patients	605 patients and additional matched 524 patients	25
Cancer Agnostic (NCI-60 cell line panel)	474 refined to 10 by systems biology methods	48 cell lines	852- Breast 73- Pancreas 270 -GBM TCGA 60- NSCLC 92- HNSCC 14- Rectal 12- Esophagus 42- Melanoma	15, 17, 109-113, 149
Breast	51	16 cell lines and 343 patients	228 patients	22
Prostate	24	196 patients	330 patients	24
Breast	4	191 patients	112 patients	23
Breast	248	168 patients	139 patients	107
Cancer Agnostic (NCI-60 cell line panel)	31	60 cell lines	1045-TCGA Breast 463- TCGA GBM 263- Glioma	99-101
Head and Neck	5 (miRNA)	2 lymphoblastic cell lines with ATM alteration from single patient	435-HNSCC TCGA	102
Head and Neck (HPV-)	13	86- TCGA HNSCC 32 HNSCC cell lines 128- TCGA HNSCC (HPV-)	44 HNSCC patients 63 HNSCC (HPV-) 5 HNSCC cell lines 59 cell lines (NCI-60)	103
Head and Neck (HPV-)	7	130 patients	121 patients	104
Esophageal	41	152 patients	31 patients	26
Gastric	11	371- TCGA Gastric	371 patients (cross-validated from training)	108
Soft Tissue Sarcoma	26	253- TCGA Sarcoma	101 patients (cross-validated from training)	105
Cervical	7	25 patients	N/A	106

Key: ATM = ataxia telangiectasia mutated, GBM = glioblastoma multiforme, HNSCC = head-and-neck squamous cell carcinoma, HPV = human papilloma virus, miRNA = microRNA, NCI = National Cancer Institute, NSCLC = non-small cell lung cancer, TCGA = The Cancer Genome Atlas

ago.[5] Following this discovery, other somatic alterations have been identified in various tumors, which has formulated the notion that genetic alterations may be targeted in specific tumors. Notably, analysis of genomic data from patient tumors has provided opportunity to develop targeted agents against various proteins controlling kinases to epigenetic modulators.[6] Additionally, the development of therapeutic monoclonal antibodies (mAb) has transformed oncologic care, most recently by modulating the host immune response to tumors.[7] Many of these targeted agents have been employed in unselected metastatic cohorts, although tumor profiling has been able to separate responders from nonresponders based on intrinsic tumor features. Various trials employing molecular profiling have begun, though to date, no prospective trial has demonstrated a benefit to selecting targeted agents based on tumor genomic make-up.[8]

In contrast to targeted therapy selection, determination of the optimal radiation regimen may require a different approach. Ionizing radiation does not have a distinct "target," but distributes its effect in the cell via a stochas-

tic manner causing damage to DNA, organelles and cellular membranes.[9] Additionally, at the tumor level, radioresponsiveness is influenced by other treatment parameters, including dose-volume relationships, total dose, fractionation pattern and type of radiation. In support of the latter, recent studies highlighted molecular differences in tumor cell radiosensitivity between dense and sparse ionizing rays[10] and various dose per fraction regimens.[11]

Some of the first studies evaluating a molecular basis for radiation sensitivity were related to normal tissue toxicity in patients with alterations in ataxia telangiectasia mutated (ATM),[12] which supported a DNA damage basis for intrinsic radiosensitivity. Numerous observations in single nucleotide polymorphism (SNP) analyses and experimental manipulations of DNA damage repair (DDR) modulators have supported this model, yet no clinically actionable genetic alteration has been validated.[4] Interestingly, patients with rare genetic syndromes driven by compromised DDR pathways demonstrate a spectrum of responses, suggesting that a single alteration in core DDR machinery may not be a sole determinant of radioresponsiveness.[13] Yard et al profiled more than 500 cell lines and identified interconnectedness between DDR protein alterations and genomic stability, which governed intrinsic radiosensitivity.[14] This study underscores the polygenic trait of radiation sensitivity.

Attempts to model the polygenic nature of radiation sensitivity have continued to emerge in recent years. One of the first studies to address this question was by Eschrich et al, who identified a cancer-agnostic diverse gene network, which modeled the cellular survival following 2 Gy in 48 cancer cell lines.[15] This network was reduced to 10 hub genes, from which a multigene expression signature was derived, termed the radiosensitivity index (RSI). The RSI has predicted for clinical outcomes in various patient cohorts treated with radiation,[16] and recently Scott et al demonstrated that substitution of a tumor-specific RSI value for the alpha variable in the linear quadratic model derives an actionable tumor feature termed the genomically adjusted radiation dose (GARD),[17] which can stratify clinical outcomes in patients treated with radiation.[18,19]

Others have hypothesized that tumor type-specific evaluation of radiation sensitivity may provide more robust classifiers compared to cancer-agnostic approaches, although some have suggested that despite heterogeneous sites of tumor origin, a common transcriptional program may regulate radiosensitivity.[20,21] **Table 1** is a nonexhaustive list of gene signatures developed to infer radiosensitivity. For instance, in breast cancer, Speers et al derived a transcriptional signature based on survival after 2 Gy in breast cancer cell lines and a patient cohort that predicted for local control in patients treated with radiation,[22] and Tramm et al identified a 4-gene signature that predicted for postmastectomy radiation benefit.[23] Similarly, the postoperative radiotherapy outcome score (PORTOS), a 24-gene signature in prostate cancer, has been validated as a predictive tool for assessing distant metastasis risk following postprostatectomy radiation.[24]

Combining gene signatures representing distinct biological processes may also improve the robustness of clinical classifiers. For example, Cui et al developed independent radiosensitivity and antigen processing/presentation signatures in breast cancer cohorts and found that integration of these signatures improved outcome stratification.[25] Zhang et al also found that integrating a 31-gene signature with the RSI, both derived similarly from the NCI-60 cell line panel, improved predictive ability in esophageal cancer patients.[26]

Interestingly, many signatures proposed to delineate intrinsic radiosensitivity show little overlap, if any, with regard to gene sets. Is this due to a broadly conserved transcriptional program resulting from genotoxic stress or is there redundancy in the information of gene signatures? Despite publication of various gene signatures representing diverse biologic processes (eg, hypoxia, epithelial-mesenchymal transition, cell proliferation), prior studies have identified similarities in the predictive ability of diverse gene sets in a single dataset for similar clinical endpoints. For instance, Fan et al found a high concordance for nonoverlapping gene signatures in breast cancer, suggesting a common biologic underpinning.[27]

Few studies investigating relationships between gene signatures and clinical outcomes prove the specificity of the derived signature by testing against a negative control signature. A study by Venet et al found that gene signatures unrelated to cancer biology (ie, effect of postprandial laughter, skin fibroblast localization, social defeat in mouse brains) were associated with overall survival in a breast cohort and found that only 18 of 47 (40%) signatures from the literature had the ability to outperform random signatures of similar size.[28]

Functional redundancy of many gene signatures argues that robust statistical methods, including random permutation of genes selected to represent signature modules, are needed to avoid spurious associations with clinical outcomes.[29] As the number of gene signatures continues to grow, it is important to interrogate the biology of individual genes composing the signature since sophisticated bioinformatics analyses can overcome real biologic differences and ultimately lead to no downstream utility.[30]

There are several important limitations to consider when implementing genomic-based strategies in clinical medicine. A major concern is the use of single-biopsy-site, tumor-profiling data to infer overall tumor biology. Tumors have significant spatial and temporal heterogeneity,[31,32] often with

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opposing prognostic gene expression profiles or targetable mutations in different tumor regions. Although heterogeneity is evident, selection of many targeted therapies and clinically useful gene signatures is informed by single-region analyses,[33] suggesting that the calculated signal in the readout may represent central biology in the tumor. Tumor profiling adds an additional level of complexity compared to signatures derived from cell cultures due to heterogeneous cell populations contributing to tumor composition. Aran et al found that noncancerous cell populations contribute to gene expression profiles and following adjustment for tumor purity, variation in differentially expressed genes and pathway enrichments were lost; this study emphasizes the need to correct for tumor purity.[34]

Another important feature to consider is the assumption that a snapshot of tumor biology derived from a single biopsy is representative of biology as treatment progresses. Myriad evidence demonstrates adaptive changes following exposure to various treatments.[35,36] For example, radiation has been shown to induce alternative splicing,[37] which has the potential to increase transcriptome diversity. Another example of adaptation is in prostate cancer cells exposed to enzalutamide, which results in differential expression of genes regulating inflammation and various metabolic processes.[38] Thus, assuming an iso-effect response to each fraction of radiation may not provide a complete picture of the dynamicity in a responding tumor.[39]

Lastly, and of utmost importance, is the required external validation of derived signatures before adoption into clinical practice. Rigorous testing in prospective randomized clinical trials or prospectively collected retrospective analyses of previous phase III trials are required to demonstrate robustness of the signature outside of the training and nonprospectively collected validation cohorts. The utility of genomic-based approaches in radiation has lagged as none of the aforementioned signatures have withstood scrutiny of the protective regulatory barriers needed to safeguard patients from implementation in clinical decision-making.

Radiomics: A Noninvasive Means to Assess Tumor Biology

Routine medical imaging, including computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET), is paramount to the diagnosis, treatment and follow-up of cancer patients.[40] Radiation oncologists approach data supplied by these anatomical and functional images differently than diagnostic radiologists, in that images are used to plan dose distributions that cover gross disease or regions at risk for spread. Although qualitative assessment by radiologists provides useful diagnostic information, each image contains a plethora of features that may be used for precise radiation delivery and treatment selection.

Radiomics refers to high-throughput extraction of quantitative image features from standard-of-care images, such as CT, MRI and PET followed by relation to biologic or clinical endpoints.[41-43] This noninvasive process allows for the ability to describe tumor characteristics while accounting for spatial and temporal heterogeneity.[44,45] Radiomics has the capacity to detect medical imaging phenotypes that are reflective of tumor features at the cellular level, with a prime example being 18-fluorodeoxyglucose PET (FDG-PET) representing glucose uptake.[41] Also, data obtained from quantitative image analysis can identify novel tumor features that complement clinical or genetic characteristics, thus improving the understanding of tumor biology.[43] Radiomics has potential to be a powerful tool to personalize clinical-decision algorithms, and novel methods continue to emerge for utilization in radiation therapy.

The workflow of radiomics involves several steps, including image acquisition, segmentation of the regions of interest (ROI), extraction of descriptive features, predictive modeling, and validation; each of these steps pose unique challenges described further below.[42,45]

Image Acquisition

The first step of radiomics involves acquiring standard-of-care images. Although lack of standardized imaging protocols across institutions does not significantly affect clinical utilization, these diverse protocols do impact extraction of quantitative features. Heterogeneous source data increase the probability for noise interference, calibration error and unfruitful analyses. For this reason, nonstandardized multi-institutional radiomics can pose major challenges. There have been recent attempts to address this issue through standardization of the imaging protocol, including the Quantitative Imaging Biomarkers Alliance (QIBA) and the Quantitative Imaging Network (QIN).[46,47]

Segmentation of Regions of Interest

The next step is segmentation of ROIs to determine which pixels/voxels within the image are to be analyzed. This step has been called the most challenging and contentious component of radiomics, and the segmentation process varies greatly across studies.[42] The process can be conducted manually, which can introduce bias through user variability[48] or can potentially be semi- or fully automated with newer approaches.[49,50]

Extraction of Descriptive Features

Radiomic features can be divided into spatial (static) and temporal (dynamic) features. Static features are derived from shape, volume, voxel intensity and texture, whereas dynamic features represent changes in kinetics

with time-varying protocols.[51] Semantic features, commonly used in radiology to qualitatively describe images (eg, spiculation, cavitation, necrosis), can be time-consuming to capture and do not provide more granular data for statistical modeling. Ongoing efforts with machine-learning methods strive to increase inter-reader agreement, lower variance, and augment more rapid data acquisition for semantic features.[52] Agnostic features, which quantitatively describe heterogeneity within the ROI (eg, wavelets, textures, histogram characteristics) can provide statistical inter-relationships between voxels and reveal hidden patterns. These features can be calculated by various texture matrices (eg, gray-level co-occurrence, neighborhood gray tone difference matrix); for a more thorough description of feature calculation please see the recent article by Rizzo et al.[53]

The feature extraction process is variable across institutions with recent attempts to address this issue. The Image Biomarker Standardization Initiative (IBSI) is an international collaboration that works to standardize extraction of image biomarkers.[54] Additionally, an open platform termed Computational Environment for Radiological Research (CERR) has been introduced to improve reproducibility, speed and clinical integration of radiomics research.[55,56] Other open-source software to extract features includes RaCaT and LIFEx.[57,58]

Predictive Modeling and Validation

Following feature extraction, data interrogation via manual statistical analysis or machine learning, is conducted to test for relationships between features, clinical endpoints or other questions of interest in a training model. Model building from a small sample size relative to the number of features can result in reduced accuracy and risk of overfitting. This potentially may be obviated by predetermining subsets of features to analyze or removing highly correlated variables, yet there are notable statistical considerations when analyzing large datasets.[59,60] Model validation, both internal and external, is a necessity for radiomics studies. Ideally, a successful model will perform similarly in training and validation cohorts. Beyond the scope of this article, Park et al provide a useful guide to assess model performance in radiomics.[61] When constructing predictive models with multivariable analysis, guidelines from transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) can help maintain reproducibility and transparency.[62]

Clinical Applications

Radiomics can significantly impact clinical decision-making within oncology,[42,45,63] including radiation.[64] Due to the vast number of recent radiomics studies, indicated by a 50% increase in published studies between 2017 and 2018,[65] we have highlighted a subset with potential to personalize radiation therapy **(Table 2)**.

Prognostication

Numerous studies have shown the utility of radiomics in stratifying clinical outcomes. Aerts et al demonstrated a CT-based radiomics signature, which captured heterogeneity and had significant prognostic value in lung and head-and-neck cancer.[41] Another recent study found that a subset of features extracted from planning CT and cone-beam CT (CBCT) scans are interchangeable, and CBCT-based signatures were prognostic for lung cancer survival.[66]

Treatment Response

Radiomics has the potential to predict radiation therapy response. A recent study demonstrated that a PET-based model developed with machine-learning improved prediction of primary refractory disease in Hodgkin lymphoma.[67] Also, Abdollahi et al developed an MRI-based model that predicted radiation therapy response for prostate cancer patients.[68] Another CT-based model based on lymph node phenotypic features was predictive of pathologic response after neoadjuvant chemoradiation in lung cancer and outperformed primary tumor feature sets.[69] Zhang et al combined 5 MRI radiomic features to distinguish radiation necrosis from tumor progression in brain metastasis treated with the Gamma Knife (Stockholm, Sweden).[70] Similarly, a T2-weighted MRI classifier outperformed qualitative assessment in diagnosing complete response in rectal cancer patients after neoadjuvant chemoradiation.[71] Another CT-based signature outperformed physicians in identifying early changes associated with local recurrence after stereotactic ablative radiation therapy (SABR) for early stage lung cancer.[72] Clearly, radiomics modeling in assessing treatment response is an area with future utility.

Treatment Planning

Another exciting area is the potential to improve radiation treatment planning and target selection. Quantitative image analysis allows for the identification of spatially explicit and distinct subregions, or habitats, of the tumor.[73] These habitats may be the result of unique intratumor selection mechanisms and have been shown to have some clinical significance. For example, Cui et al demonstrated that MRI multiregion analysis outperformed conventional prognostic factors in glioblastoma[74] and Wu et al showed subregions in PET and CT images were also more robust in predicting lung tumor control than commonly used prognostic parameters.[75] Rathore et al developed an MRI signature, which provided *in vivo* estimation of spatial extent and pattern of tumor recurrence within peritumoral edema of glioblastoma; these high-risk areas

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Table 2. Selected Radiomics Studies with Potential to Personalize Radiation Therapy Delivery

Cancer	Imaging Modality	Study Endpoint(s)	Number of Patients	Conclusion of Analysis	Clinical Application	Reference
Prostate	MRI	Diagnosis	381	MRI-based radiomics models outperformed PI-RADSv2 in distinguishing cancerous vs non-cancerous tissue or high- vs low-grade disease	Diagnosis	114
NSCLC	PET	OS	Training: 262 Validation: 50	FDG-PET radiomics from tumors and nodes can improve prognostication for NSCLC	Prognostication	115
GBM	MRI	OS	79	Multiregion quantitative analysis of MR images has prognostic utility for GBM and outperformed conventional prognostic factors	Prognostication	74
NSCLC	CT	OS, FFDM, LRC	107	Radiomics features change due to radiation therapy and end of treatment values may be indicators of treatment response	Prognostication	116
Prostate	MRI	Biochemical recurrence	74	Radiomic analysis of MRI predicted biochemical recurrence following radiotherapy	Prognostication	117
GBM	MRI	OS, PFS	Training: 126 Validation: 165"	Radiomic analysis had significant prognostic value for OS and PFS in patients with recurrent GBM receiving bevacizumab	Prognostication	118
Rectal	MRI	LR, DM, DFS	Training: 67 Validation: 34	Delta radiomics via MRI predicted clinical outcomes after chemoRT and surgery as an independent prognostic factor	Prognostication	119
GBM	MRI	PFS, OS	181	Radiomics improved prognostication for patients beyond molecular, clinical, and standard imaging	Prognostication	98
GBM	MRI	OS	Training: 75 Validation: 37	Deep-learning-based radiomics model was able to generate a prognostic imaging feature-based biomarker for OS prediction	Prognostication	120
NSCLC	CT	OS, RFS, LR-RFS	59	CT-based radiomics prognosticates OS and progression as early as 3 months after SBRT	Prognostication	121
NSCLC	PET/CT	OS, DSS, RC	150	Radiomics predicts control and survival for patients with lung cancer treated with SBRT	Prognostication	122
Head and Neck	PET/CT	LRC, DM	300	Models combining radiomic and clinical variables had significant prognostic utility for LRR and DM in patients treated with chemoRT	Prognostication	123
NSCLC	CT	OS	Training: 132 Validation: 62 and 94	Subset of radiomic features from CT and CBCT images are interchangeable and a previously described radiomics signature is prognostic for OS	Prognostication	66
NSCLC	PET/CT	DM	Training: 70 Validation: 31	PET imaging characteristics were significantly prognostic for the development of distant metastasis in patients with early stage NSCLC	Prognostication	75
Esophageal	CT	OS	36	Post-treatment texture analysis was predictive of survival, and the combination of pretreatment texture parameters and maximum wall thickness performed better than morphologic tumor response	Prognostication	124

Key: chemoRT = chemoradiation, CT = computed tomography, CBCT = cone-beam CT, DFS = disease-free survival, DM = distant metastasis, DSS = disease-specific survival, DCE-MRI = dynamic contrast-enhanced MRI, EGFR = epidermal growth factor receptor, FFDM = freedom from distant metastasis, GBM = glioblastoma multiforme, HNSCC = head and neck squamous cell carcinoma, HPV = human papilloma virus, IMRT = intensity-modulated radiotherapy, LR = local recurrence, LRC = locoregional control, NSCLC = non-small cell lung cancer, MRI = magnetic resonance imaging, OS = overall survival, pCR = pathologic complete response, PET = positron emission tomography, PFS = progression-free survival, PI-RADS = Prostate Imaging-Reporting and Data System, RC = regional control, RFS = relapse-free survival, SBRT = stereotactic body radiation therapy

Table 2. Selected Radiomics Studies with Potential to Personalize Radiation Therapy Delivery (continued)

Cancer	Imaging Modality	Study Endpoint(s)	Number of Patients	Conclusion of Analysis	Clinical Application	Reference
GBM	MRI	OS	32	MRI spatial variations defined regional habitats in GBMs, and the distribution of these varied significantly among the different survival groups	Prognostication	125
Cervical	PET, MRI	LRC	Training: 69 Validation:33	Radiomics from MRI and PET predicted recurrence and LRC with higher prognostic power than clinical parameters	Prognostication	126
NSCLC	CT	Molecular discrimination OS	57	Radiomic features from preoperative CT images were significantly associated with mutational profiles in lung squamous cell carcinoma	Prognostication Radiogenomics	127
Head and Neck	CT	Molecular discrimination LC	Training: 93 Validation: 56	Heterogeneity of HNSCC tumor density is associated with LC after chemoRT and HPV status	Prognostication Radiogenomics	95
Prostate	CT	Gleason score	342	CT-based radiomics model was able to accurately distinguish high risk from low risk and Gleason score >7 vs 3+4 vs 4+3	Prognostication Radiogenomics	128
Head and Neck NSCLC	PET/CT	Molecular discrimination OS	Training: 474 Validation: 545	PET/CT-based radiomic signature was significantly prognostic for OS; radiomic features significantly associated with different gene sets	Prognostication Radiogenomics	41
Nasopharyngeal	MRI	Therapy response	Training: 100 Validation: 23	MRI radiomics predicted response and survival and in combination with clinical data, showed excellent predictive performance	Prognostication Treatment Response	129
Hepatocellular	CT	LR	106	A robust radiomic signature (one signal feature) predicted LR and OS after radiation	Prognostication Treatment Response	130
Colorectal	CT	Molecular discrimination OS, PFS	64	Combining contrast-enhanced CT radiomics with gene expression and histopathologic factors provided improved prognostication	Radiogenomics	97
Head and Neck	PET/CT	Molecular discrimination	53	Combining p16 and Ki-67 staining with PET/CT textural features helps determine PD-L1 expression	Radiogenomics	94
Renal cell	CT	Molecular discrimination	45	Machine-learning based quantitative CT texture analysis predicted PBRM1 mutation status	Radiogenomics	131
GBM	MRI	Molecular discrimination	Training: 69 Validation: 40	Preop MRI features predict for PTEN mutation	Radiogenomics	96
NSCLC	CT	Molecular discrimination	298	CT-based radiomics of lung adenocarcinomas predicted presence of EGFR mutations in Asians	Radiogenomics	93
Prostate	MRI	Molecular discrimination	17	Radiomic features correlated with gene expression	Radiogenomics	132
Breast	MRI	Proliferation	377	Quantitative radiomics features from DCE-MRI were associated with Ki67 expression	Radiogenomics	133
Breast	MRI	Molecular discrimination	922	Machine learning radiomics model, based upon DCE-MRI features, predicted for receptor status	Radiogenomics	91

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Table 2. Selected Radiomics Studies with Potential to Personalize Radiation Therapy Delivery (continued)

Cancer	Imaging Modality	Study Endpoint(s)	Number of Patients	Conclusion of Analysis	Clinical Application	Reference
Breast	MRI	Molecular discrimination	84	Radiomic image phenotypes were strongly associated with the triple negative subtype	Radiogenomics	134
Breast	MRI	Molecular discrimination	47	Quantitative analysis of MR imaging identified associations with activation of various molecular pathways (tyrosine kinase signaling, immune)	Radiogenomics	135
NSCLC	PET	Molecular discrimination	348	EGFR appears to drive metabolic tumor phenotypes that are captured in PET images, whereas KRAS mutations do not	Radiogenomics	92
Prostate	MRI	Toxicity	30	Early structural change analysis may contribute to predict postradiotherapy fracture	Toxicity	136
NSCLC	CT	Toxicity	32	Radiomic features can classify and predict who will develop immunotherapy-induced pneumonitis	Toxicity	137
Esophageal	CT	Toxicity	106	Radiomics can provide a quantitative, individualized measurement of patient lung tissue reaction to radiation and risk of pneumonitis	Toxicity	79
Nasopharyngeal	CT	Toxicity	35	Radiation-induced acute xerostomia can be predicted by saliva amount and CT changes	Toxicity	81
NSCLC	CT	Toxicity	14	Radiomics features correlated with physician-scored post SBRT lung injury and showed a significant dose-response relationship	Toxicity	80
Nasopharyngeal	CT	Toxicity	21	Volume and textural feature changes on CT during radiation treatment predict for parotid shrinkage	Toxicity	82
Head and Neck	CT	Toxicity	Training: 22 Validation: 4	Mid-treatment parotid gland changes evidenced by CT radiomic analysis substantially improved the prediction of late radiation-induced xerostomia	Toxicity	83
Breast	MRI	Subclinical disease	146	Preoperative MRI textural features improved the prediction of sentinel lymph node metastasis	Treatment Planning	138
Prostate	MRI	Gleason score prediction	48	Multiparametric MRI-based radiomics was able to generate stable Gleason score probability maps	Treatment Planning	139
GBM	MRI	Regions at risk	90	Multiparametric MRI pattern analysis assists with in vivo estimation of the spatial extent and pattern of recurrence in peritumoral edema, which can guide resection or radiation dose escalation	Treatment Planning	76
Esophageal	CT	Subclinical disease	197	CT-based radiomics signature significantly associated with lymph node metastasis	Treatment Planning	140
Prostate	MRI	Regions at risk	23	Radiomics-based framework is able to generate a targeted focal treatment radiation plan	Treatment Planning	78
Head and Neck	MRI	LRC	14	MRI subvolumes at baseline, which persist during early course of chemoRT and predict for failure, could identify opportunity for local dose boost	Treatment Planning	77
Bladder	CT	Subclinical disease	Training: 80 Validation: 38	Preoperative CT-based radiomic nomogram accurately predicted lymph node metastasis	Treatment Planning	141

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Table 2. Selected Radiomics Studies with Potential to Personalize Radiation Therapy Delivery (continued)

Cancer	Imaging Modality	Study Endpoint(s)	Number of Patients	Conclusion of Analysis	Clinical Application	Reference
Head and Neck	PET/CT	Segmentation	40	PET/CT-based textural characterization discriminates between normal and abnormal tissue	Treatment Planning	142
Rectal	MRI	pCR	114	T2-weighted sequence analysis is more predictive of pCR after chemoRT vs qualitative assessment	Treatment Response	71
Brain Metastases	PET	Toxicity vs Progression	47	Textural feature analysis may have potential to discriminate brain metastases and radiation injury	Treatment Response	143
NSCLC	CT	LR	45	Radiomics detects early changes associated with LR that are not typically considered by physicians	Treatment Response	72
Brain Metastases	MRI	Toxicity vs Progression	87	Delta radiomics can distinguish between radiation necrosis and tumor progression after radiosurgery	Treatment Response	70
Prostate	MRI	Gleason score and stage	35	Machine-learning-based models predicted IMRT response, Gleason score and stage	Treatment Response	68
Cervical	MRI, PET	Tumor response to treatment	21	Tumor heterogeneity varies between patients, modalities, and timepoints, and some features are associated with favorable response	Treatment Response	144
NSCLC	CT	Tumor response to treatment	85	Lymph node phenotypic information predicts for treatment response with a higher performance than radiomic features from the primary tumor	Treatment Response	69
Rectal	MRI	pCR	186	Pretreatment radiomics nomogram can predict pCR in locally advanced disease	Treatment Response	145
Gastric	CT	Response to radiation	43	Pretreatment radiomic analysis can predict pulsed low-dose radiation response	Treatment Response	146
Hodgkin Lymphoma	PET	Unresponsive tumors	251	PET radiomics model improved upfront patient stratification, predicting primary refractory disease as well as those who were successfully salvaged vs those who died from disease	Treatment Response	67
NSCLC	CT	Response to radiation	20	Daily CT scans during radiation can be used to assess for early treatment response	Treatment Response	147
Breast	MRI	pCR	35	Heterogeneity within tumor subregions associated with fast washout on DCE-MRI predicted pCR after neoadjuvant chemotherapy	Treatment Response	148

Key: chemoRT = chemoradiation, CT = computed tomography, CBCT = cone-beam CT, DFS = disease-free survival, DM = distant metastasis, DSS = disease-specific survival, DCE-MRI = dynamic contrast-enhanced MRI, EGFR = epidermal growth factor receptor, FFDM = freedom from distant metastasis, GBM = glioblastoma multiforme, HNSCC = head and neck squamous cell carcinoma, HPV = human papilloma virus, IMRT = intensity-modulated radiotherapy, LR = local recurrence, LRC = locoregional control, NSCLC = non-small cell lung cancer, MRI = magnetic resonance imaging, OS = overall survival, pCR = pathologic complete response, PET = positron emission tomography, PFS = progression-free survival, PI-RADS = Prostate Imaging-Reporting and Data System, RC = regional control, RFS = relapse-free survival, SBRT = stereotactic body radiation therapy

may be optimal targets for dose intensification.[76] Similarly, Wang et al utilized dynamic contrast-enhanced MRI to identify subvolumes of primary head-and-neck tumors at increased risk for local failure.[77] Recently a multimodule framework called radiomics-based targeted radiation therapy planning (RadTRaP) was created, which employs MRI data, deformable image registration, and a feature-based dose plan.[78]

Toxicity

Radiomics also has the capacity to assess for and predict radiation-induced toxicity. Cunliffe et al identified changes in serial CT features that are associated with radiation dose and development of radiation pneumonitis.[79] Another study identified CT-based texture features significantly correlated with dose and lung injury severity after SABR.[80] Others have found that observed changes in radiomics-based measures (delta radiomics) over the course of radiation therapy predict for parotid gland shrinkage and xerostomia.[81-83]

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Utility of Radiogenomics

There are 2 definitions of "radiogenomics" in the literature: 1) the study of genetic variation associated with radiation therapy response,[84,85] and 2) the study of the relationship between gene expression patterns and imaging phenotypes;[86,87] we refer to the latter.

One application of radiogenomics is to identify tumor imaging correlates of specific genomic attributes, which may provide a noninvasive alternative to biopsy.[88,89] Multiple recent studies have shown the ability for MRI-based features to predict molecular subtypes and hormone receptor status in breast cancer.[90,91] Other studies have demonstrated that radiomics can predict the presence of epidermal growth factor receptor (EGFR) mutations by PET features[92] and CT features.[93] Additionally, radiomics may be able to predict programmed death-ligand (PDL1) expression,[94] human papilloma virus (HPV) status[95] or a *PTEN* mutation.[96]

Others have shown that integrating radiomic and genomic data into a single model can improve prognostic power. For example, Badic et al used CT features and gene expression in colorectal cancer to improve patient stratification[97] and Kickingereder et al found that an MRI signature combined with molecular and clinical data improved outcome prediction in glioblastoma.[98]

Pathways to Clinical Application

Genomic medicine has provided substantial insights into tumor biology and this has been exploited by medical oncologists in several facets of clinical practice and trial development.[152] An advantage medical oncology has over radiation oncology in utilizing genomic information, is access to numerous biomarker panels with established FDA-approved targeted therapies. In contrast, commonly, radiation is an "add-on" modality in genomic-based trials, such as those with Oncotype Dx (TAILOR RT; NCT03488693), targeted therapies (NCT03667820), conventional chemotherapy (NCT03609216) or immunotherapies.[154] Although not formally developed to assess radiation efficacy, several molecular classifiers are being employed in breast cancer to make decisions for treatment intensification or omission.[153]

Our institution is planning to initiate the first genomic-based prospective clinical trials to guide radiation therapy dose in early 2020. As part of this effort, RSI is being established in the CLIA molecular laboratory at Moffitt, which will allow us to use RSI and GARD in clinical trials. Our initial focus will be in head and neck cancer where we will use RSI/GARD to guide radiation dose de-escalation for HPV-positive head and neck cancer patients. A second trial in triple negative breast cancer will utilize the RSI/GARD model to decide whether patients should receive a boost to the tumor bed following whole-breast radiation.

Radiomics has the potential to significantly improve precision medicine in the diagnosis, prognostication, and treatment planning for cancer patients. However, the current literature is limited by its retrospective nature, as well as significant heterogeneity between studies. To improve the quality, standardization, and reproducibility of future studies, Lambin et al developed the radiomics quality score (RQS), a homogeneous evaluation criterion that assesses radiomics studies based on 16 key components.[45,151] Vallieres et al emphasized the importance of designing high-quality, fully transparent, and accessible studies to improve the clinical translation of radiomics.[150] Ongoing prospective clinical trials are investigating the utility of radiomics to inform clinical decision-making in the treatment of hepatocellular carcinoma (NCT03917017), prostate cancer (NCT03979573), and head-and-neck cancer (NCT03953976, NCT02666885). A trial in lung cancer plans to prospectively collect PET/CT data to predict response to immunotherapy (NCT04007068). However, further prospective validation, using the RQS as a guideline, is required to fully realize the potential of radiomics.

Conclusion

Big data analytics is rapidly progressing and demonstrates enormous potential to change the oncologic decision-making landscape. As improvements continue in bioinformatics, image analysis, statistical/machine learning models, and end-user experience with data interpretation, integration into the clinical workflow of a radiation oncologist is bound to occur soon. Genomics and radiomics provide an opportunity to increase the precision of radiation delivery in selection of dose and spatial delivery. Our field should openly embrace these tools and take the needed steps away from a "one-size-fits-all" philosophy.

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