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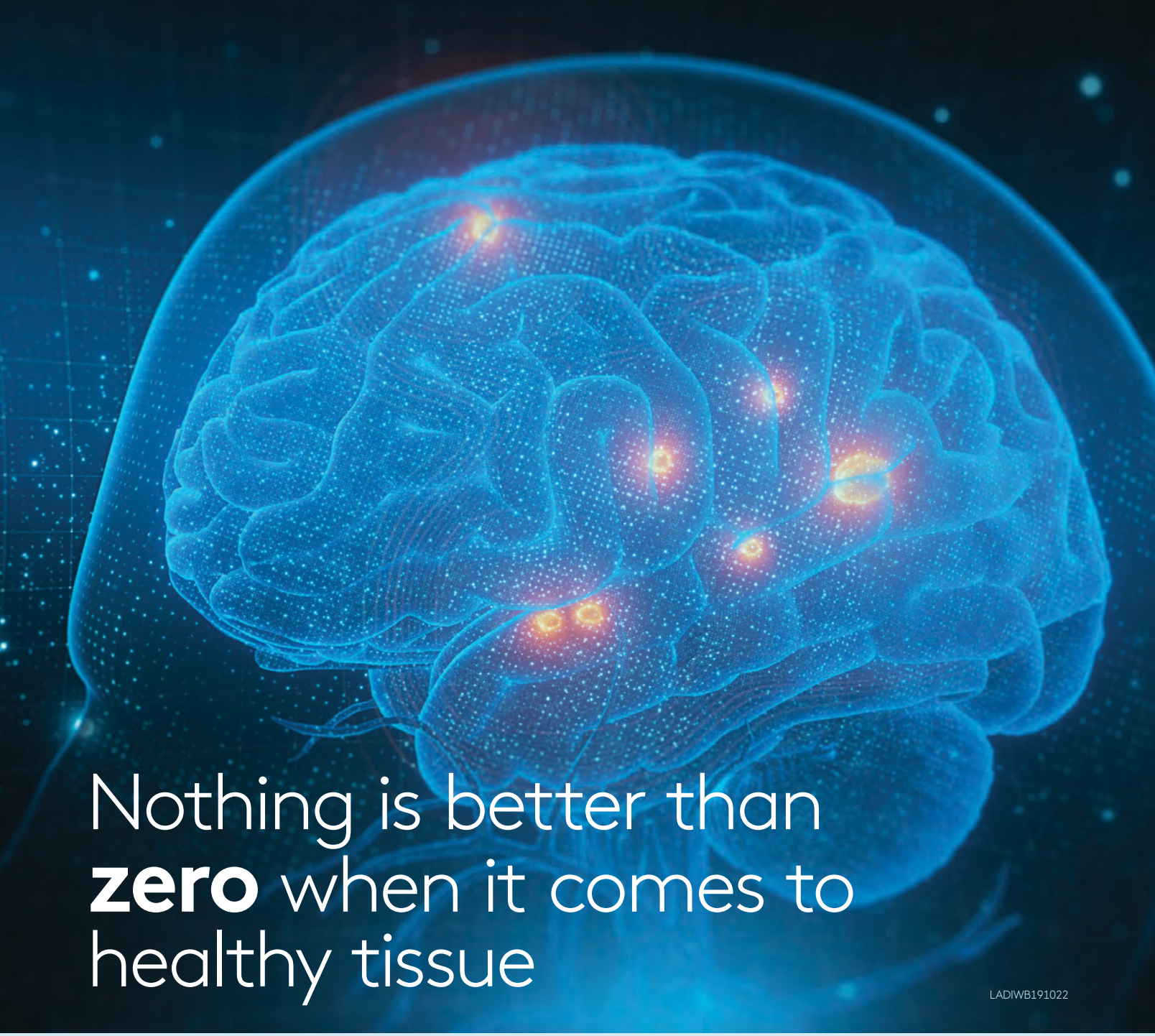

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FOCUS: RADIOMICS

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DEPARTMENTS

Erratum

In the article, *The global radiation oncology workforce in 2030: Estimating physician training needs and proposing solutions to scale up capacity in low- and middle-income countries* [Appl Radiat Oncol. 2019; 8(2):10-16], figure 3 inadvertently contained duplicate information. The corrected figure 3 can be found at https://cdn.agilitycms.com/applied-radiation-oncology/PDFs/issues/ARO_06-19_Elmore.pdf.

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EDITORIAL

More than meets the eye: Radiomics in radiation oncology

John Suh, MD, FASTRO, FACR
Editor-in-Chief

Radiomics, the theme of this month's issue, is poised to significantly improve informed decision-making in radiation therapy delivery—an exciting future that is swiftly becoming reality in everyday practice. Even more promising is the integration of radiomics with data such as molecular, metabolic and microenvironmental tumor analytics. Together this information can fuel precision diagnostics and theranostics on an individualized level, as described in the enlightening review article, *Genomics and radiomics: Tools to see the unseen to personalize radiation therapy*. A second review delineates the potential of radiomics in lung cancer treatment. This insightful overview, *An emergent role for radiomic decision support in lung cancer*, explains how radiomic models offer immense possibility for personalized lung cancer diagnosis, risk profiling, and treatment by assimilating image characteristics undetectable to the human eye. We hope you find these articles, both of which offer free SA-CME credits, helpful in understanding and embracing personalized medicine in radiation oncology.

Rounding out the theme is the Technology Trends feature, *The intersection of radiomics, artificial intelligence and radiation therapy*. Here, leading experts examine the need for reproducibility, standardization, safeguards, and collaboration across disciplines and institutions to optimize radiomics.

We are also pleased to present the thoughtful Global Perspectives column on cultural complexities and their effects on radiation medicine in Beirut, as recounted by an ARRO Global Health Scholar. Global health challenges and solutions are further addressed in the case report, *Use of an OP Care smartphone application to improve care of gynecology cancer patients in a low-resource setting*. The authors describe the feasibility and efficacy of mobile technology to enhance patient record storage, treatment monitoring, appointment scheduling and tracking, and more in a clinic in Botswana, Africa. A second case report describes a patient with recurrent, poorly differentiated cutaneous squamous cell carcinoma metastatic to the right orbit and his complete response to pembrolizumab immunotherapy. A third case report discusses the unusual event of strip alopecia in two patients who received high-dose, VMAT-based stereotactic radiosurgery.

Lastly, we are proud to feature the Resident Voice editorial on the important topic of leadership development. As the author urges, we need to squelch the belief that leadership training is only for those who want to head a committee or department, and usher in awareness, tools and training for all radiation oncology residents during this formative point in their career. My strong opinion is that every physician should develop their leadership acumen given our influence with patients and society.

As 2019 ends and 2020 begins, we extend our deepest gratitude to you for your support over the last 8 years. We are proud to have greatly expanded our editorial offerings, peer review panel, advisory board, SA-CME articles, followers, and collaborators since our inception, and look forward to a new year of continued growth, service, and inspiration.

Dr. Suh *is the editor-in-chief of* Applied Radiation Oncology, *and professor and chairman, Department of Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.*

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RESIDENT VOICE

Leadership development: Why is it important for radiation oncology residents?

Shauna R. Campbell, DO

Shauna R. Campbell, DO

Medicine is a unique career in which, regardless of formal titles, all physicians will be considered leaders. After more than a decade of higher education one may presume that physicians entering independent practice have received formal instruction on effective leadership, but too often that is not the case. Leadership development was traditionally an investment in those who demonstrated characteristics of "natural born leaders" chosen for positions of authority. However, as our expectation of leadership has evolved, so should our approach to training and development. The authoritative leadership model has been replaced by a collaborative vision of leading through influence.[1]

Despite growing awareness of the importance of leadership development, it remains sparsely integrated into graduate medical education, and is infrequently included in radiation oncology residency specifically. Leadership development should be regarded as a part of lifelong learning, recognizing its ability to positively impact physician development. Radiation oncology training affords four years for developing leadership skills at a critical point of a young physician's career.

Professionalism, interpersonal skills, and communication are core competencies of resident education and important components of leadership, but there is more. Suppose there is a skill that correlates with resident wellness, performance, and decreased burnout. Should we be teaching that? What if that skill is also associated with quality improvement and patient outcomes? Emotional intelligence is an integral part of leadership development that can be taught, measured, and positively impacts all of the above.[2-4] Implementing a leadership development program takes considerable investment, but the results can be influential in the short and long term.

Dr. Campbell *is a resident physician at the Cleveland Clinic, OH.*

Despite growing awareness of the importance of leadership development, it remains sparsely integrated into graduate medical education.

The Cleveland Clinic residency program has been innovative in its creation of a leadership curriculum within the formal curricular structure. Leadership training takes place during semi-annual group retreats scheduled during regular clinical hours. The focus of retreats includes self-awareness, team-building, principles of effective communication, cultural development, and operational leadership.[5] As residents, we participate in both individual and group activities that facilitate strength finding, the understanding of leadership styles, and the learning of effective communication skills to enable conflict management. These daylong retreats are well received by residents and often followed by an enjoyable group bonding activity such as axe throwing, doing an escape room challenge, and volunteering with local organizations.

Failing to incorporate formal leadership development into residency training is a missed opportunity. Every physician is a leader and providing basic training during residency prepares new graduates to be effective leaders. We need to remove the notion that leadership training is for those interested in heading a committee or department and instead provide the stable framework upon which new graduates can more effectively manage their clinical practice. The future of medicine will be value-based, patient-centered care, and the new generation of radiation oncologists will need the leadership skills to guide our field through this transition.

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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.

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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-

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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

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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

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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
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

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

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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

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

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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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AN EMERGENT ROLE FOR RADIOMIC DECISION SUPPORT IN LUNG CANCER

Description

This review article discusses recent developments in radiomics (a computational image evaluation technique that integrates medical images, clinical data, and machine learning) its applications to lung cancer treatments, and the challenges associated with radiomics as a tool for precision diagnostics and theranostics. Discussion examines methodology, data collection, segmentation, feature extraction, feature selection, predictive models, validation, application, data sharing, data standardization, model evaluation and model interpretation. Despite hurdles to implementation, radiomic models show immense potential for personalized lung cancer diagnosis, risk profiling, and treatment due to their ability to incorporate image characteristics beyond the ken of the human observer.

Learning Objectives

After completing this activity, participants will be able to:

1. Understand the means by which radiomics models are developed in order to identify and apply the strengths and weaknesses of each model.
2. Gain greater insights into the potential applications of radiomics in guiding diagnosis, radiation planning, and radiation dose predictions for patients with lung cancer.
3. Encourage potential end users to participate in the development of these tools to more appropriately guide their clinical use.

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An emergent role for radiomic decision support in lung cancer

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Medical images represent anatomical and/or functional facsimiles of the human body. As such, they serve a critical role in the diagnosis of diseases and the evaluation of treatment response. Current interpretations of the images by radiologists comprise an anthropogenic synopsis of 2-dimensional (2D) or 3-dimensional (3D) spatial data. Despite extensive efforts at standardization, evaluations continue to depend on the individual evaluating the images, resulting in variation of interpretation.

Radiomics is an emergent methodology within image analysis in which quantitative data is acquired using automated analysis techniques (Figure 1).[1-4] The extracted information, also known as image features, can be combined with orthogonal data (eg, clinical data or biological measures [ie, mutations, transcriptomic panels, etc.]) to build prediction models for diagnosis or treatment selection. These strategies are poised to offer a more quantitative and objective basis for informed medical decision-making.[1,5,6]

The tripartite mainstays of cancer treatment include radiation therapy, chemotherapy, and surgery. These treatments extensively utilize medical images for diagnosis and to monitor efficacy. The imaging modalities most commonly used include computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). The frequent utilization of these technologies provides clinical practices, even those with modest patient volumes, an extensive collection of mineable image data. Indeed, radiomics features have already been associated with improved diagnosis accuracy in cancer,[7] specific gene mutations,[8] and treatment responses to chemotherapy and/or radiation therapy in the brain,[9,10] head and neck,[11,12] lung,[13-17] breast,[18,19] and abdomen.[20] More recently, radiomics features integrated into a multitasked neural network were combined with clinical data to derive a personalized radiation dose for patients treated with stereotactic lung radiation therapy.[21] Altogether, these developments suggest that the integration of image data to inform clinical care is on the horizon.

Herein, we review recent developments in radiomics, its applications to lung cancer treatments, and the challenges associated with radiomics as a tool for precision diagnostics and theranostics.

Methodology

A general workflow of radiomics is depicted in Figure 2. At the data collection stage, imaging data is combined with clinical and histopathological data. Image data must undergo additional steps before downstream analyses, however, including region-of-interest segmentation, and feature and texture extraction. Based on the classification task at hand (eg, local failure after radiation, progression-free survival after immunotherapy, etc.), researchers can then proceed to the next stage, the training and validation of the radiomics model. After training and validation, a dataset that the algorithm has not yet seen (test or holdout set) is used to evaluate the model. If the model is shown to be accurate, it may potentially provide clinicians with improved decision-making

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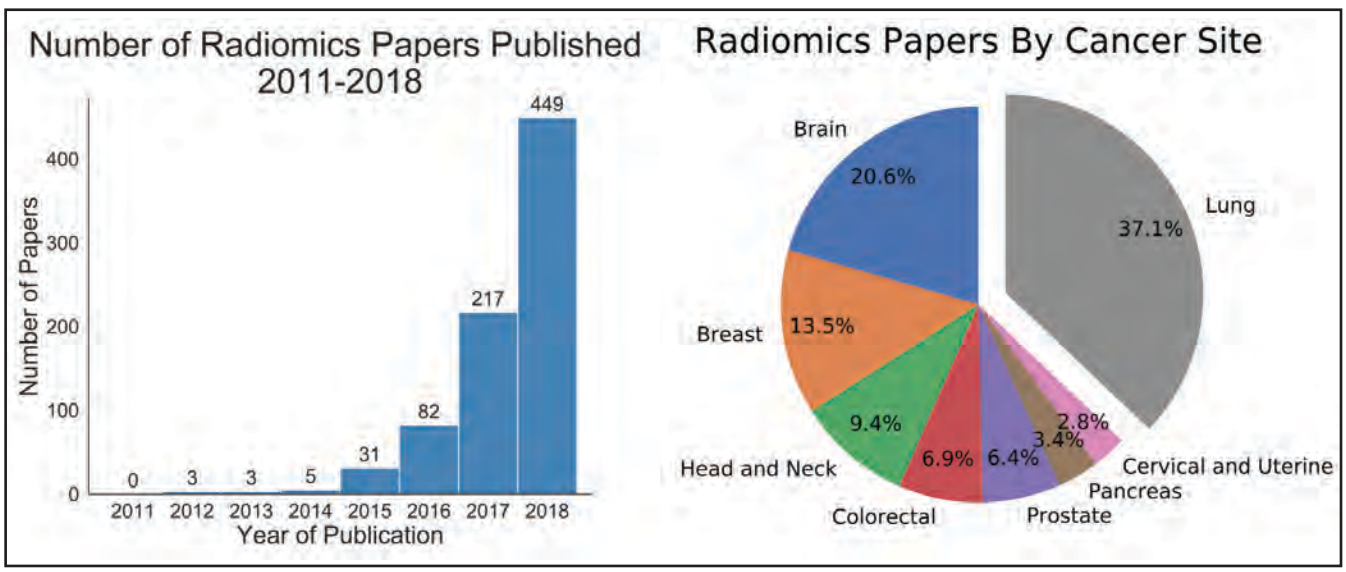

FIGURE 1. *The number of published manuscripts in radiomics has significantly increased in the last several years, representing growing interest and development in this field.*

capabilities. Transportability testing (using a dataset from a distinct but plausibly related population) of the model is also critical since it can help determine whether the model can be implemented more broadly in other settings. To establish transportability, an independent dataset external to the primary institution should be used.

Data Collection

The first step in radiomics is data acquisition. A large sample size is required because of the complexity of the prediction task. Since machine learning and neural network-based models can learn multifactorial, nonlinear relationships between image-based predictors and outcomes, models can inadvertently too closely fit or "memorize" the data they are built on. This can lead to poor performance on previously unseen data, a phenomenon known as overfitting. To mitigate overfitting, large datasets and other strategies are implemented to build improved and more generalizable models.

Although first developed using CT images, radiomic methodologies have also been implemented for other modalities such as MRI, PET, and ultrasound (US). Models are usually built on a single modality to ensure the consistent treatment of images in the preprocessing pipeline. Images and clinical data used to build a radiomic model can be gathered from single or multiple institutions. To ensure standardization among the data presented to the model, there are critical quality assurance steps at both the data acquisition and preprocessing steps. Standardization of imaging protocols and having a clearly defined, universally applicable preprocessing pipeline are critical for model reproducibility.

At the time of imaging, acquisition and reconstruction parameters such as voxel size and gray-level discretization are central to achieving reproducible results. Other factors that may affect stability of radiomic features include respiratory motion and use of IV contrast. It has been previously shown that inter-CT scanner variability[22] and variability of random noise[23] may affect the stability of radiomic features. To decrease variability of the features during the collection process, resampling and image cropping to a uniform spacing and size prior to extracting features is recommended.[24-26] Another data optimization technique involves clipping and normalizing voxel intensities. Lastly, data augmentation through preprocessing transformations or data generation using neural networks can increase the data available to a nascent radiomic model.[27]

Segmentation

Delineation of the tumor and normal tissue is a crucial first step in both radiation therapy and radiomics, directly influencing the performance of radiomic models.[28] Appropriate segmentation is critical to models that extract predefined features directly, as well as to neural models, which can be trained to emphasize the designated areas. Identifying the section of the image to be used for segmentation and extraction of radiomic features is a topic of ongoing investigation. Traditionally, features are extracted from the segmented tumor region. However, there is also increasing interest in image characteristics adjacent and external to the gross tumor volume. For example, Dou et al[29] have shown the possibility to improve multivariate models to predict the risk of distant metastasis by extracting features from the peritumoral region.

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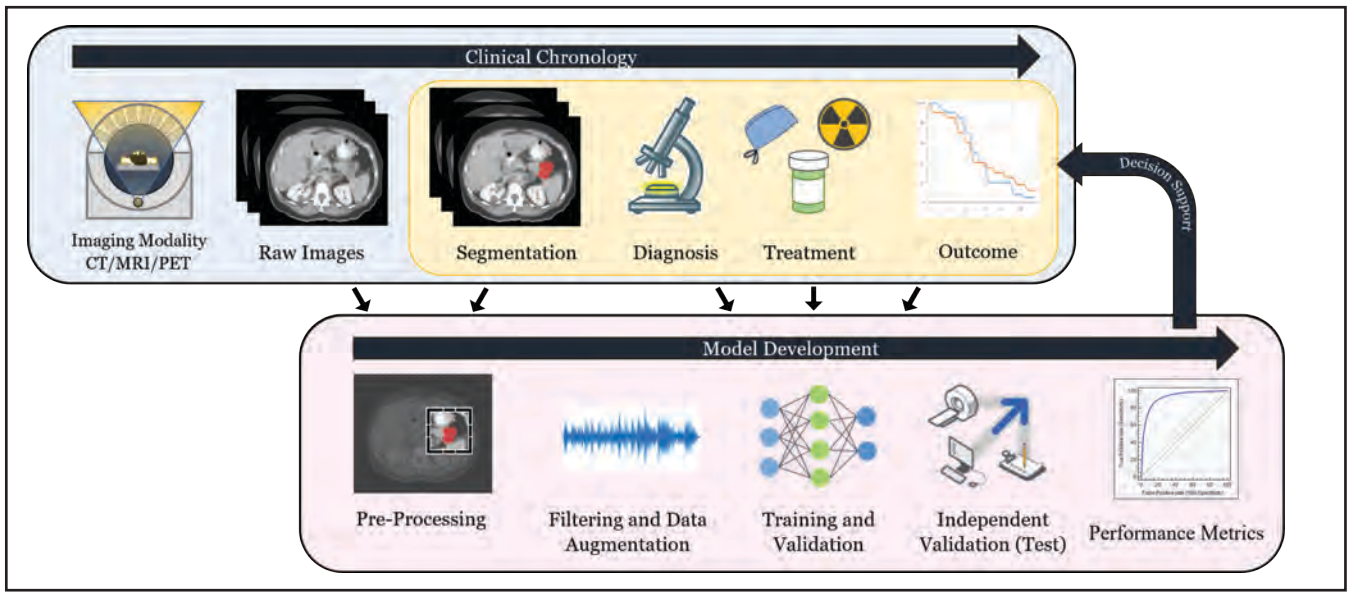

FIGURE 2. *The process of constructing a radiomic model occurs in parallel with patient imaging, diagnosis and treatment. Once finalized, the model informs each of these areas, which rapidly develop. Advancements in these areas are highlighted in this paper.*

There are certain obvious challenges with manual segmentation: Tumors may be near tissue with similar characteristics, making it difficult to distinguish between the two structures. Moreover, medical images may have distortions due to random noise, imaging resolution, and artifacts. To reduce intra- and interobserver variability, automatic or semi-automatic segmentation may improve the stability of radiomic features. Various methods have been proposed for semi-automatic segmentation.[30,31] With recent advances in deep-learning algorithms, fully automatic segmentation methods have also been developed.[32]

Feature Extraction

Originally, radiomic models were developed from predefined, "hand-crafted" features consisting of algebraic representations of voxel intensities. This structured data can be analyzed with classical statistics or with machine learning and neural networks. More recently, convolutional neural networks have been implemented to directly learn properties of the image, allowing for the extraction of features beyond those conceived and crafted by humans. Aspects from either or both methodologies can then be merged into a representative quantity (or quantities) known as an image signature.

Features can be categorized based on origin. Semantic features are those currently used in clinical practice as visualized and described by the radiologist. Radiomics complements these with nonsemantic, quantitatively and systematically extracted features, based on voxel intensity. Classic quantitative radiomic features can be further categorized as structural, first, second, and higher order. Structural features are the most basic descriptive and derived measures such as tumor volume, shape, maximum diameter, and surface area. These features can help quantify tumor spiculation and other factors that may indicate tumor malignancy. First-order features refer to simple statistical quantities such as mean, median, and maximum gray-level values found within the segmented tumor. Extracting second-order, or textural features, quantifies statistical inter-relationships between neighboring voxels. This provides a measure of spatial relationship between the voxel intensities in the tumor, which may allow for the determination of tissue heterogeneity.[33] Higher-order statistical features are extracted by applying filters and transformations to the image. Two of the most popular methods are the Laplacian transforms of Gaussian-filtered images and wavelet transforms. Such higher-order methods increase the number of features extracted by the order of magnitude of filters applied. This allows identification of image attributes based on various spatial frequency patterns. Lastly, incorporating the change in radiomic features over time, or delta radiomic features, has been shown to improve lung cancer incidence,[34] overall survival, and metastases prediction.[35]

Deep learning, a subset of machine learning, uses a neural network model that mimics the connectivity of a biological brain to identify complex abstractions of patterns using nonlinear transformations. Neural network models learn directly from unstructured data such as images through convolutional layers that synthesize voxel intensities into representative features. Deep-learning approaches typically require more data, a challenge that can

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be mitigated through various techniques such as data augmentation[36] and transfer learning.[37]

Feature Selection

Manual feature extraction can result in thousands of radiomic features, some of which are redundant. In a dataset with clinical events (eg, local failure after radiation therapy) occurring at much lower magnitudes, inclusion of large-scale parameters with low event rates can contribute to model overtraining or overfitting. Utilization of feature selection techniques can help alleviate this potential pitfall.

Radiomic feature selection methods focus on stability of features, feature independence, and feature relevance. The stability of features may be analyzed with a test-retest dataset in which multiple images of the same modality are taken over a relatively short period to test whether such features are reproducible.[38] Feature independence is assessed by statistical methods testing the correlation between the features themselves, such as principal component analysis (PCA). Feature selection based on relevance can be done with a univariate approach, testing whether each individual feature is correlated with the outcome being investigated, or a multivariate approach, which analyzes the combined predictive power of the features.

Parmar et al[11] used clustering as a method to contend with the large number of quantitative features. The high-dimensional feature space was reduced into radiomic clusters, with clusters being predictive of patient survival, tumor stage and histology. Alternatively, neural networks have been shown to learn increasingly detailed geometries in each subsequent convolutional layer, and can be used to generate a set of highly descriptive image features.[39]

Development of Predictive Models

A predictive model is then constructed from the extracted relevant features creating a "radiomic signature." Depending on the task at hand, various prediction models can be utilized (eg, classification and survivability models). Classification models categorize data into known categories (eg, tumor is benign or malignant). Survivability models require additional time-related information about the patients being treated, and aim to predict the time to failure or survival of patients undergoing a certain treatment. One approach to predict time-to-event clinical outcomes is by making the image signature equivalent to the logarithm of the hazard ratio in a Cox regression model.[21,40] Other machine-learning methods can then be used with either manually extracted features or the outputs of neural network models to derive prediction scores.

Validation

To show that the radiomic model is generalizable, it must be validated. Model validation on an independently obtained external dataset is recommended. The model is usually analyzed using the receiver operating characteristic (ROC) curve with the area under the curve (AUC) being the commonly reported value in discrimination analysis. Model validation should be repeated on a target population prior to its deployment to ensure transportability.

Challenges and Opportunities

The rapid proliferation of radiomics applications has fueled optimism that medical images can be utilized to better guide clinicians in the recommendation of optimal treatment strategies. As with every technique and technology, however, certain challenges require attention to create and implement a robust radiomics model.

Data Sharing

Collecting and sharing data over multiple institutions or hospitals is a significant limitation to model development and testing. A single institution or hospital typically does not have enough events to establish and test a transportable radiomics model. To address this need, multiple data-sharing networks have been established to house shared data such as the Cancer Imaging Archive[41] and the Quantitative Imaging Network.[42] Contributions of well-annotated data to the shared datasets or collaborations between multiple institutes are critical for future model development and implementation.

Data Standardization

In multi-institutional radiomics studies, it is rare that all institutes share the same imaging acquisition settings such as imaging modality, protocol, or reconstruction algorithm. Additionally, image segmentation and interpretation of the data may be highly subjective and prone to human variations. While a highly standardized dataset will more likely guarantee a consistent model and reproducible predictions, this is an impractical expectation of a large dataset, especially in a multi-institutional setting. Data cleaning and preprocessing can mitigate these challenges through selection of similarly annotated images, image resampling, retrospective segmentation, and even translation of one modality to another.[43] Additionally, the robustness of radiomic models built on multi-institutional datasets can be inherently higher since they are less prone to overfitting caused by a single institutional standard.

Model Evaluation

Although radiomic models may be highly performant on the data on which they are built, prediction results may be affected when implemented into real clinical settings due to model under-or overfitting. Therefore, it is crucial to use independent, external datasets to evaluate the predictive power of the established radiomic signature. Additionally, the radiomic model should be trained on new data as the standard of care continues to

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improve for it to adapt to new treatment protocols and prognosis, as well as to better quantify its accuracy. A reliable method to maintain an up-to-date radiomics model can be as critical as establishing the initial model. As data-sharing archives[41,42] (noted above) become more prevalent, the need for large volumes of current, external images will be met. Since radiomic models can be deployed through online or locally hosted software, they are highly movable even if the independent data on which they are evaluated is not.

Model Interpretation

Since radiomics is a fairly new concept and model structures are inherently abstruse (representing a black box), questions and concerns are often raised toward the ultimate implementation of radiomic models. Physician skills and intuition are honed over years of training and experience. There is anticipated to be a gulf of trust between physicians' "gestalt" and experience-driven approaches with the current difficult-to-interpret output of artificial intelligence systems. Efforts to improve the interpretability of predictive models include feature selection through bootstrapping[44] as well as development of saliency maps highlighting the relative importance of voxels to the predicted outcome.[21] The implication that radiomic models manifest underlying biology by being able to classify histological subtypes[45,46] and gene mutations[47,48] makes the association between genetics and radiomics an active area of research. This type of integrative analyses of known risk factors is needed to explain the meaning of radiomic features. Promoting enhanced interpretability of radiomic and neural-network-derived models will be a critical step to catalyze implementation as a decision-support tool.

Potential Applications

A growing number of studies show the value of radiomics as a tool to augment clinical decision-making, with significant progress in applying radiomics to lung cancer diagnosis, treatment, and risk evaluation.

Investigative Models

Aerts et al[38] created a radiomic signature prognostic of overall survival in independent cohorts of patients based on intensity, shape, textural, and wavelet features. The features were selected based on stability using test-retest CT scans, independence, and univariate predictive capability of the features before constructing a multivariate model including the top feature from each of the four feature groups. Several radiomics studies have shown diagnostic potential in CT-based models to discriminate cancerous tumors from benign nodules.

A number of studies have also applied radiomics to predict histology based on pretreatment CT images[45,46] and radiogenomics to identify the tumors' underlying gene expression.[47,48] Currently, histological classification and genetic subtyping depend on biopsies and re-biopsies. If radiomics methods achieve clinical levels of accuracy, it may allow patients to forego numerous invasive biopsies. For example, Wang et al[47] showed that it is possible to create a deep neural network using CT images to provide an accurate method to establish epidermal growth factor receptor (EGFR) status in lung adenocarcinoma patients, potentially reducing the need for biopsy.

Another set of studies looked at the prognostic and predictive possibilities of using the radiomic approach—an important area in precision medicine because it informs the creation of an optimal treatment plan. Such studies predict probability of response to treatment,[49] survival,[50,51] and risk of metastases.[29,52]

Extending classification and survivability models to guide treatment, Lou et al[21] developed an image-based, deep-learning framework for the individualizing of radiation therapy dose. First a risk score was identified by a deep neural network, Deep Profiler. This signature outperformed classical radiomic features in predicting treatment outcome. This framework also incorporates a model to project optimized radiation dose to minimize treatment failure probability.

Hosny et al[36] trained deep neural networks to stratify patients into low- and high-mortality risk groups, and were also able to outperform models based on classical radiomic features as well as clinical parameters. The neural network predictions were largely stable when tested against imaging artifacts and test-retest scans. In addition, there was a suggestion that deep-learning extracted features may be associated with biological pathways including cell cycle, DNA transcription, and DNA replication.

Altogether, radiomics could potentially serve an important complementary role to other orthogonal data such as genetic and clinical information to improve assessment of clinical characteristics and molecular information.

Deployment

The models discussed have translation potential because they could be integrated into clinical practice upon additional and prospective validation. Imaging is a mainstay of clinical use, and software deployment of radiomic models are noninvasive and, if designed with user input, can be seamlessly integrated into daily workflow for the intended specialist (eg, radiologist or radiation oncologist).

There are a several avenues of implementation for software facilitating radiomic analyses into routine clinical practice. These include improved segmentation through semi-automatic or automatic contouring, which can be achieved by traditional image analysis techniques such as region-growing,[30,31] convolutional techniques such as neural network-based segmentation,[32] or "smart-contouring" techniques based

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on the regions of an image determined to be salient based on a deep-learning model.[21] Another promising area for integration is risk-profiling. Modeling risk can be achieved through a software package paired with an institution's existing imaging server. This should minimize significant disruption of the existing clinical workflow. As with any method of risk-profiling, predictive radiomic models could serve as an advisory decision-support tool in the hands of the radiologist and radiation oncologist. Specifically, radiomic models that both model and mitigate the risks are poised to alter the clinical paradigm(s). Adjusting treatment strategies through dose-specific[21] or targeted agent-specific recommendations represent possible uses that could improve clinical outcomes in select patient populations. As with segmentation and risk-profiling, these applications can be achieved through software deployment.

Lastly, while other biomarkers are likely to represent critical orthogonal inputs to more accurately predict clinical outcomes, it is possible that tumor intrinsic determinants (ie, genetic alterations, RNA gene expression, etc.) can be detected by radiomic features, as suggested.[38,53] Additional studies that seek to determine whether these classes of variables (image vs biology) are tautological, orthogonal or somewhere in between will be critical to assessing the need for additional inputs into the models. Convergence toward an integrative approach that incorporates these varied inputs is likely unavoidable in order to improve model accuracy and ultimate clinical deployment.

Conclusions

Radiomics is a computational image evaluation technique that integrates medical images, clinical data, and machine learning. Despite hurdles to implementation, radiomic models show immense potential for personalized lung cancer diagnosis, risk profiling, and treatment due to their ability to incorporate image characteristics beyond the ken of the human observer.

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Radiation therapy elective in Beirut: A brief insight into the challenges of radiation delivery in Lebanon

Osama Mohamad, MD, PhD

Having spent my entire medical and residency training in the US, I was fortunate to receive the Association of Residents in Radiation Oncology (ARRO) Global Health Scholar Award and spend a month as a visiting resident in the Department of Radiation Oncology at the American University of Beirut Medical Center (AUB-MC) in Lebanon.

To describe my experience during the elective, I would like to start by introducing Lebanon and AUB-MC. Lebanon is a small country (10 452 sq km) along the Mediterranean coast in the Middle East (**Figure 1**). According to data from the World Bank, Lebanon is classified as a middle-income country.[1] While exact numbers are unfortunately unavailable due to complex sociopolitical reasons, most recent estimates indicate a Lebanese population of more than 6 million, including over 2 million refugees (1.5 million Syrians and 0.5 million Palestinians).[2] With respect to cancer statistics in Lebanon, the GLOBOCAN 2018 report estimates about 17 294 new cases of cancer (242 cases per 100 000) and 8976 deaths due to cancer in 2018.[3] While overall cancer care in Lebanon is significantly better than that of many countries in the region, the quality of care is region- and hospital-dependent with remarkable variations in access to care (including significant variations in screening and preventive cancer programs), medications (including chemotherapies and/or immunotherapies), imaging, and radiation therapy technologies. In addition to out-of-pocket expenses, the medical bill in Lebanon is shared by the social security fund (which does not cover all citizens), the Ministry of Public Health, and private insurance. In an already struggling economy plagued by political corruption, modern feudalism,

FIGURE 1. *Map of the Middle East showing the geographic proximity of Lebanon, Syria and Iraq. Credit: Wikimedia Commons contributors, "File:Syria-Iraq-Lebanon location map.svg," Wikimedia Commons, the free media repository, https://commons.wikimedia.org/w/index.php?title=File:Syria-Iraq-Lebanon_location_map.svg&oldid=266603958 (accessed November 6, 2019).*

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FIGURE 2. *Aerial view of Beirut showing the American University of Beirut (AUB). The inset (in red) shows the AUB Medical Center (AUB-MC) (A). The main entrance of the AUB-MC is pictured (B), and the radiation oncology department is one story below ground level. New buildings of the AUB-MC vision 2020 medical complex are also shown (C). AUB-MC vision 2020 is an ambitious initiative aiming to expand current medical facilities and provide state-of-the-art patient care services, medical teaching, and biomedical research to citizens of the Middle East. Photos from www.aub.edu.lb and www.aubmc.org.lb*

total neglect of natural resources, and decades of regional and civil wars, the influx of hundreds of thousands of refugees from nearby war-torn countries has strained the economy even more and added more pressures on the healthcare system in Lebanon.

AUB-MC was originally established in 1902 as a 200-bed hospital associated with the Syrian Protestant College (later known as AUB) and has grown to become a remarkable hospital and medical school with superior patient care, medical research, and medical education earning it accreditations from the Joint Commission International and the Accreditation Council for Graduate Medical Education International (**Figure 2**). AUB-MC has always strived to provide exceptional patient care in the community and the region. Similar to the efforts of the University Hospital in general, the Department of Radiation Oncology has provided exceptional radiation therapy services to thousands of patients since the 1960s even during times of extreme violence from the civil war. Currently, the department is staffed by 5 radiation oncologists, most of whom were trained in the United States, and 4 physicists/dosimetrists. This team manages an operation that uses 2 linear accelerators to deliver world-class 3-dimensional conformal radiation therapy, image-guided radiation therapy, intensity-modulated radiation therapy, stereotactic body radiation therapy, and high dose rate brachytherapy, among others, to treat about 70 to 80 patients a day, while training 4 radiation oncology residents (typically 1 resident per year). In addition, the radiation oncology department at AUB-MC staffs the Nabatieh Governmental Hospital (NBGUH), a public community hospital housing a single linear accelerator and providing the only radiation therapy unit in the south of Lebanon (2 governorates). In addition to AUB-MC, there are about 12 operational linear accelerators in 7 radiation therapy centers in Lebanon, with 2 or 3 centers in the planning or construction phases. Based on the International Atomic Energy Agency (IAEA) recommendation for needing 1 linear accelerator for every 500 new cancer cases in any country[4] and assuming 17 294 new cases (see above), Lebanon needs about 34 linear accelerators to meet the demand of its cancer patients. Zeidan and Geara provide a good review of the status of radiation therapy in Lebanon.[5]

During my 1-month stay at AUB-MC, I attended daily resident teachings (physics and clinical case conferences), weekly chart rounds, multiple tumor boards, and I shadowed attendings in their daily clinics (both at AUB-MC and NBGUH). The radiation oncologists at AUB-MC typically see all kinds of malignancies but since the team had recently expanded to 5 attending physicians, the trend has shifted to some degree of specialization within the department. Radiation oncologists, residents, physicists, nurses and therapists at AUB-MC are capable of delivering treatment plans adherent to international guidelines while at the same time operating with tight resources and little time. Having been trained at the University of Texas Southwestern in Dallas, it was interesting to see radiation treatments performed with less dependence on daily image guidance and custom mold cushions, and with significant savings in treatment time. Another interesting aspect of practicing radiation oncology and medicine in general in Lebanon is the culture and stigma around the diagnosis of cancer. This cultural paradigm makes it difficult for physicians to navigate some cases. For example, it was not too uncommon to have families visit our clinic without the patients because families worry that the emotional burden of the diagnosis may affect the patient's response to treatment.

The most interesting aspect of my brief visit was observing Iraqi cancer patients traveling from Iraq to get treated in Lebanon. Once regarded as a model healthcare system in the region with excellent infrastructure and universal coverage, decades of tyranny, regional wars, foreign invasion, terrorism, civil unrest, neglect, and deeply rooted corruption in all national institutions, Iraq's health care system is now fragmented and unable

to provide appropriate medical care, let alone cancer care, to Iraqi citizens. This instability has led to a significant lack in funds, critical infrastructure, and professional personnel, making optimal healthcare delivery unfeasible. Violence did not spare doctors, leading to the death, kidnapping, and forced immigration of many specialists, causing a significant drop in the number of oncologists and radiation specialists in most provinces including the capital Baghdad.[6] Of special oncologic and humanitarian significance in Iraq is the use of depleted uranium-based weaponry during the Gulf Wars, which allegedly increased the incidence of malignancies in many communities.[7] Additionally, years of embargo against the Saddam Hussein regime meant that many cancer treatments and technologies (including but not limited to chemotherapies and linear accelerators) did not reach Iraqi citizens for fear that the regime would use them to synthesize chemical weapons. Most recently, the health consequences of the 2003 invasion of Iraq were devastating[8] and the influx of immigrants from nearby Syria compounded the problems.[9] With respect to radiation oncology services, a recent report indicated the presence of 18 mega-voltage machines (35% of the ideal number of machines recommended by the IAEA), and 76 radiation specialist physicians (20% of the recommended number).[10] Accordingly, Iraq is clearly unable to meet the demands of its cancer patients and it is no surprise that Iraqi citizens flee to neighboring countries for cancer treatments.

Every Iraqi patient I met had a unique story, but all stories shared similar elements such as poor access to care in their home country; lack of appropriate care (wrongful diagnoses or wrongful treatments) leading to disease exacerbation; and national security concerns, which ultimately prompted travel to Lebanon with the hope of cure. As stated above, Lebanon does not have enough radiation therapy resources to meet the needs of its own citizens. Still, many institutions in Lebanon, including AUB-MC, are absorbing these additional needs and providing care to Iraqi patients. The trip to Lebanon, however, is exhausting physically, financially, and emotionally to the patients and their families. Unfortunately, Iraqi patients pay a portion of the medical bill out of pocket in addition to costs of living (housing, food, and transportation) in Lebanon. Many patients have witnessed significant delays in their care and did not have an appropriate or full medical workup in Iraq, which often meant additional costs and more treatment delays in Lebanon. Often, patients receive part of their care in Lebanon (such as radiation) and resume the remaining portions of their treatment plan (such as chemotherapy) in Iraq, leading to suboptimal and interrupted care. I can only imagine those patients who leave Iraq for better services only to die abroad. Not only would they have paid a significant portion of their savings or sold precious belongings to get treated, but their families must also pay for the repatriation of their bodies. The current cancer care status in Iraq is intolerable and unsustainable. There is an utmost need for a long-term plan that siphons the investments from a band-aid approach to a bold plan for cancer control focusing on building cancer centers in Iraq and training local physicians to deliver appropriate care. Anything short of that is a waste of time and resources.

In conclusion, I am very appreciative of the opportunity provided by ARRO and the great time I had at AUB-MC. Everyone in the radiation oncology department, including physicians, residents, physicists, nurses, therapists, and staff, were extremely kind and generous. My time in Lebanon and the interactions I had were highly insightful. I made new friends in our field and learned new ways of delivering radiation therapy. Most importantly, I saw first-hand the suffering of patients in countries where radiation therapy is not available. There is an urgent need for radiation therapy services in low- and middle-income countries. More innovative entrepreneurial approaches supported by academicians in the field are needed to fill the void.

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The intersection of radiomics, artificial intelligence and radiation therapy

Mary Beth Massat

Defined as a method that extracts mineable data from radiographic medical images, radiomics can potentially provide information that an oncologist and/or medical physicist may not detect with the human eye alone.

As Gillies et al put it, "Radiomics are more than pictures, they are data.[1] With the increasing number of data recognition tools and the emergence of machine learning (ML) and deep learning (DL), the ability to extract information beyond visual interpretation has become a significant trend. An integral component of radiomics is the integration of ML and DL algorithms.

"We are at a watershed moment, moving away from handcrafted features to understand and develop imaging biomarkers for evaluating a patient's response to radiation therapy, to a black box approach with deep learning taking over that task," says Raymond H. Mak, MD, a thoracic radiation oncologist and associate professor of radiation oncology at Harvard Medical School, Brigham and Women's Hospital, and Dana-Farber Cancer Institute in Boston.

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Dr. Mak and Hugo Aerts, PhD, director of the Artificial Intelligence in Medicine (AIM) Program at Harvard-Brigham and Women's Hospital, are helping to lead the development of DL and radiomic technologies applied to medical imaging data. Recognizing a need for a standardized extraction engine in radiomics, AIM has developed pyradiomics, an open source platform for reproducible radiomic feature extraction. Supported in part by a US National Cancer Institute grant, Pyradiomics is based on open source tools and platforms developed by big tech companies such as Google, Facebook and others.[2]

Toward Intelligence and a Multimodality Approach

At Duke University, Kyle Lafata, PhD, a postdoctoral associate in radiation oncology and the program director for AI Imaging, Woo Center for Big Data and Precision Medicine, is working toward developing and translating quantitative image analysis techniques and digital biomarkers into actionable intelligence that can be used in clinical practice, specifically radiation oncology.

Using radiomics, features and information in medical images are extracted, including morphology (the 3-dimensional size and shape of the object), intensity distribution of the signal with an image, the texture or the relationship between voxels in an image, and the interaction of those voxels spatially.

"Images are unstructured data," Dr. Lafata explains, "so the process is to transcribe them into structured datasets that can be combined with other information to use in diagnosis or prognosis."

He adds that imaging data such as standard uptake value (SUVmax) are radiomic features; combining imaging and clinical data provides a more powerful prognostic effect than using them individually. ML/DL helps correlate the data so it can be used in clinical practice.

"One domain knowledge isn't enough—by combining integrative 'omics' we can learn more complex information," Dr. Lafata says. His

"By extracting both radiomics and pathomics data, we can start to see the appearance and behavior of disease across different spatial and functional domains."

Kyle Lafata, PhD
Duke University
Woo Center for Big Data and Precision Medicine

group has been looking at pathomics, the concept of extracting the same or similar features from digital pathology slides as they are extracting with radiomics. "By extracting both radiomics and pathomics data, we can start to see the appearance and behavior of disease across different spatial and functional domains."

For example, by taking the anatomic data from a computed tomography (CT) scan on a tumor mass with metabolic data on the F-18 fluorodeoxyglucose (FDG) uptake in a positron emission tomography scan and then combining that with features extracted from the pathology (the biopsy), Dr. Lafata can learn more about metabolism of the tumor, the structure of the tumor and the microscopic disease.

"Now, we have 3 levels of information that will tell us different things about that tumor," he adds. "Depending on the machine learning model we intend to develop, we can use that data to make a diagnosis, guide treatment or determine therapeutic response."

Dr. Lafata says a multimodality approach must extend beyond one discipline or domain, such as radiology, pathology, genetics and health information, including the electronic medical record. By combining these disciplines, the clinician may uncover enough information to define the patient phenotype diagnostically and therapeutically.

Standardization and Other Challenges

Data access and sharing are central to the collaborations among researchers and institutions. One way to expedite this process while minimizing data privacy issues is through a distributed learning environment in which models move to different institutions rather than requiring data to be in a central location, says Mattea Welch, a PhD candidate at the University of Toronto, who has co-authored several articles on radiomics as part of her doctoral studies and thesis. She has collaborated with Dr. Aerts and Ander Dekker, PhD, professor of clinical data science, MAASTRO Clinic, Maastricht University, The Netherlands.

"We are generating mass amounts of imaging data in the clinic every day, and there is potential to leverage that data, but we need to better understand what is driving the predictive and prognostic capabilities of the quantified imaging features," Dr. Welch says. "There is a need for standardized methods and collaboration across disciplines and institutes."

The intersection of computer science and medicine is not only an area of discovery, it is also where safeguards, standardization, and collaboration are needed to ensure reproducibility. This need led Dr. Welch and co-authors to highlight the vulnerabilities in the radiomic signature development process and propose safeguards to refine methodologies to ensure the development of radiomic signatures using objective, independent and informative features. These safeguards include using open source software, such as pyradiomics; testing models and features for prognostic and predictive accuracy against standard clinical features; testing feature multicollinearity using a training dataset during model development; testing underlying dependencies of features using statistical analysis or by perturbing data; ensuring image quality by preprocessing data to avoid erroneous features such as metal artifacts; and including manual contouring protocols to describe prevalent imaging signals used for delineation.[3]

"The main take-home message is that collaboration between researchers and clinicians is needed to ensure understanding of the nuances of clinical data and methods being used for radiomics," Dr. Welch adds.

Variations in systems, software and reconstruction algorithms across manufacturers and the impact on data reproducibility and prognostic capabilities is an area of concern and active research. One position, notes Dr. Welch, is that if extracted features are not stable across different systems and data perturbations, then perhaps they are not prognostic or predictive.

It also comes down to imaging systems not being engineered for intended

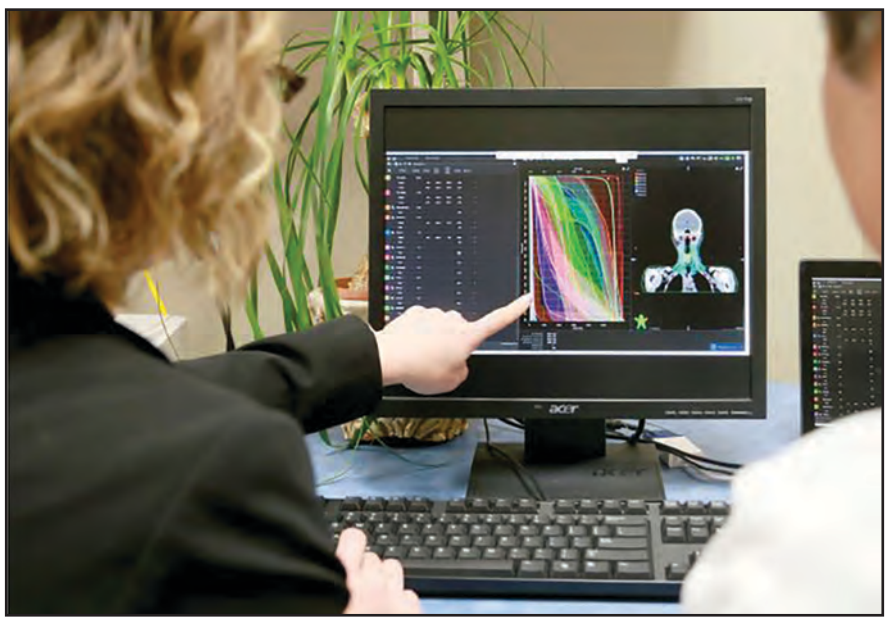

FIGURE 1. *RapidPlan by Varian combines machine learning, which generates the optimal baseline treatment plan, with user intelligence and expertise to control, personalize, and fine-tune individual plans through multicriteria optimization.*

radiomic applications. "Now, we are treating images as data. It's a reverse engineering process. Since we are now using these systems in nontraditional ways, we need them to be more quantitatively sound. For example, if we want to use radiomics to differentiate a benign vs a malignant tumor, then we need to make sure the features capture the underlying phenotype of the disease, and not the underlying noise distribution of the imaging system."

Additionally, different postprocessing techniques such as filter-back projection and iterative reconstruction in CT imaging can impact image quality and, therefore, the radiomic data.

"A common problem in medicine is the issue of small sample sizes," Dr. Lafata adds. "Even if we have a large data set, we need that feature data to match with the outcome to build a model. A problem across the board has been the ability to gather that robust information on each patient irrespective of having a large amount of input data for a machine learning algorithm."

Even digital biomarkers are limited by source variation and unstable data, he says. A lot of work remains to harmonize and unify data and knowledge across domains such as genomics and radiomics.

"We need to understand the intricacies of the data and the learning algorithm," Dr. Lafata says. "The uncertainty of machine learning models is not as straightforward as conventional statistical propagation of error. It comes down to the complex relationship between the data that is being measured and the response of a learning algorithm to that data."

Human Factors and Potential

"Traditional radiomics require a human for analysis," Dr. Mak says. To analyze a tumor, for example, the oncologist would manually segment it. This could present certain human biases into the data, based on the clinician's use of libraries of features and their understanding of the tumor biology. When a DL model is trained, it can learn from the underlying data without the need for initial human interpretation.

"We think that with DL we can minimize human biases. However, the chief concern is whether that DL-derived data is interpretable and what is that DL algorithm learning from?" says Dr. Mak. "Is that DL performing according to task?"

Yet, despite such concerns, Dr. Mak believes radiation oncology will continue the pursuit of applying DL-based tools to radiomics. DL and radiomics will have a role in 3 primary areas: 1) aiding diagnosis; 2) predicting treatment response and patient outcome; and 3) augmenting humans in manual tasks, such as segmentation and radiation therapy planning.

The development of automated planning has already begun. Dr. Mak was lead author on a paper describing how a crowd innovation challenge was used to spur development of AI-based auto segmentation solutions for radiation therapy planning that replicated the skills of a highly trained physician.[4]

"The potential of this type of technology to save time and costs and also increase accuracy is significant, particularly for areas of the world where this type of skill and specialty may not be available or is understaffed," says Dr. Aerts.

According to Dr. Lafata, their lab at Duke Radiation Oncology pioneered mathematical techniques to optimize treatment planning and help determine the best plan for improving dosimetric constraints. This early work inspired Varian (Palo Alto, California) to commercialize the methodology as the RapidPlan knowledge-based treatment planning solution (**Figure 1**).

"Solutions such as RapidPlan that have a human-machine interface are lower risk than one that doesn't have the human element," Dr. Lafata says.

Beyond what is commercially available, Drs. Aerts and Mak see potential

> "From the image capture to the treatment planning to dose delivery, AI is revolutionizing the field of radiation therapy. AI will impact outcome prediction and enable better monitoring response."
>
> Hugo Aerts, PhD
> Harvard-Brigham and Women's Hospital

for radiomics and AI/DL to aid treatment planning and the selection of the optimal plan as well as monitor patient response.

"Deep learning and radiomics will move beyond the traditional realm of predicting response and be applied to other aspects, such as identifying the patient's biological phenotype and serial assessment of tumor evolution in response to treatment," Dr. Mak adds.

Dr. Welch notes that some researchers are also seeking to predict toxicity using the same pattern recognition techniques as radiomics. "By quantifying the dose in different organs at risk using radiation therapy plans, we can predict toxicity or different outcomes such as loco-regional failure," she says.

Delta radiomics is another area of research in which changes in the features are calculated using pre- and post-treatment images. Then, Dr. Welch explains, those delta-radiomic features can be tested to determine whether they correlate with different patient outcomes.

"From the image capture to the treatment planning to dose delivery, [artificial intelligence (AI)] is revolutionizing the field of radiation therapy. AI will impact outcome prediction and enable better monitoring response," Dr. Aerts says.

However, he cautions that human validation should remain an important aspect of any AI or radiomics-based solution to ensure high quality. The pursuit of radiomics should involve using AI to achieve a good solution quickly and still be reviewed and approved by humans.

Several organizations are building large plan libraries and aggregate DL-based models on different data sets, Dr. Mak adds. However, the underlying concern remains that the data may not be entirely reliable, and the quality may not be the same across different data sets.

"Context is key for these radiomic and DL applications," Dr. Mak says. "There can be interpretability problems or data quality issues. The key aspect for deep learning is to have a large and well-curated data set to train the model but also context-dependent expertise to develop and ensure the appropriate clinical application."

The bottom line, says Dr. Lafata, is that while radiomics and DL are on opposite ends of the spectrum—with radiomics being a hand-crafted human approach and DL being a computerized approach—the two are complementary techniques that will enable the field of radiation therapy to interpret images and data beyond human capability and intuition.

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RADIATION ONCOLOGY CASE

Use of an OP Care smartphone application to improve care of gynecology cancer patients in a low-resource setting

Tlotlo B. Ralefala, MD; Sonya Davey, MPhil; Natalie Bonner, BS; Barati Monare, BA; Givy Dhaliwal, BS; Surbhi Grover, MD, MPH

With 10 million new cancer diagnoses expected annually by 2030, low- and middle-income countries (LMICs) are expected to see an increase of cancer incidence.[1] Currently, > 60% of the global cancer burden and 70% of cancer-related mortality occur in LMICs.[2] In these regions, there is a need for access to early detection, affordable treatment, and integrated treatment monitoring. This case summary describes the use of a smartphone application to monitor treatment initiation and follow-up of patients with gynecologic cancers who presented to the multidisciplinary team clinic (MDT) at Princess Marina Hospital, Gaborone, Botswana.

CASE SUMMARY

Following the success of 2 digital health pilot studies in LMICs[3,4] in January 2018, the clinic adopted OP Care, an outpatient smartphone application developed by ONE BCG Pty Ltd (Gaborone, Botswana, Africa). OP Care is able to: 1) store and share patient oncology records with restricted access to users, 2) electronically schedule appointments including automatic reminders to patients and notifications of missed appointments to providers, and 3) display real-time clinic reports. OP Care provides a user-friendly interface that enables physicians, nurses, and students to enter information into an electronic form and add notes and attachments. The average time to enter patient data into the application is lower than previously used paper records. The application's electronic link to Google Data Studio enables real-time deidentified reports of parameters including age, gender, HIV status, cancer type, cancer stage, treatment intent, treatment type, appointments completed, appointments missed, and short message services (SMS) sent.

From January 2018 to March 2019, OP Care was used to enroll 751 patients, of whom 506 (67.4%) were enrolled from the gynecologic MDT clinic and 245 (32.6%) were from the general oncology unit. Of all enrolled patients, 401 (53.4%) were aged 40 to 60 years, 647 (86.2%) were female, 376 (50.1%) were HIV-positive, and 437 (58.2%) were treated with curative intent therapy. Addionally, 432 (71.6%) patients were diagnosed with cervical cancer, 263 (35.0%) were stage II/III, and 61 (10.1%) had an unknown stage.

In total, OP Care tracked 1103 completed appointments and 415 missed appointments. Missed appointments are stratified by appointment type: 102 (24.6%) were follow-ups after treatment, 159 (38.3%) were for treatment review, 138 (33.3%) were generic appointments, and 3 (0.72%) were for offsite treatment.

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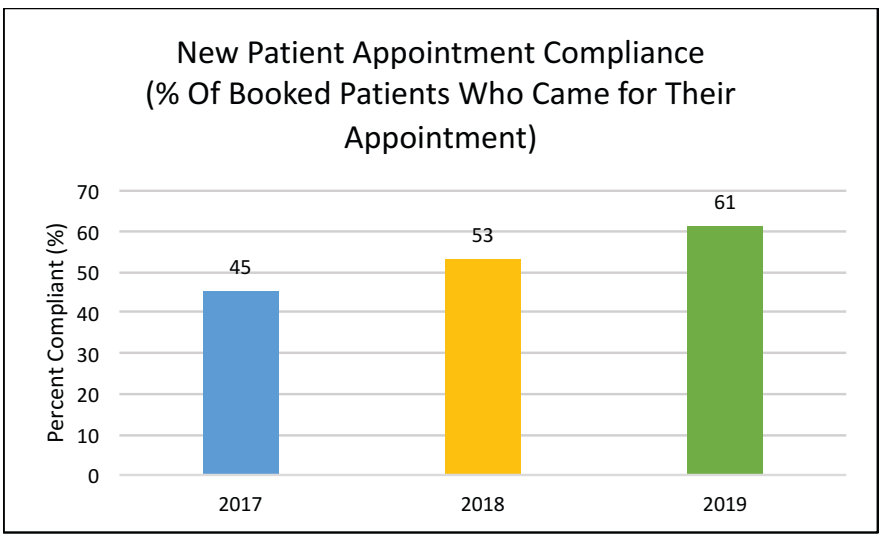

***FIGURE 1**. Compliance with new appointments since the implementation of the OP Care smartphone application.*

Unfortunately, missed appointments were not recorded in the resister for use in evaluating the compliance rate prior to OP care. During the period, 2492 short message services (SMS) were sent to remind patients of their appointments, of which 2,370 (95.1%) were successfully received by the patient on a feature phone. Of the 751 cases, < 5 patients had no cell phone of any kind and had messages sent to their care provider (eg, son, daughter).

We reviewed new patient booking data in the MDT clinic from 2017-2019 to assess whether the patient attendance rate improved with implementation of OP Care. In 2017 (May to December), before implementation of OP Care, an average of 45% of the patients :(based on a total of 561 patients) booked for clinic actually came (prior to that, data was not available since the registers were not saved). In Feburary 2018, OP Care was initiated in the clinic, with very few patients (< 1%) declining consent to enroll. In 2018, the attendance rate improved to 53%. The attendance rate for 2019, with OP Care fully implemented, from January to June, was 61%. Thus, between 2017 to 2019 (before and after OP Care initiation) there was a 33% increase in patients arriving to booked appointments, which was statistically significant using a t-test ($p = 0.02$) (**Figure 1**).

DISCUSSION

Through Botswana's national insurance system, citizens usually have access to all treatment modalities required based on cancer stage at full cost to the government. However, similar to other LMICs, oncology care in Botswana suffers from a high patient burden accompanied by a lack of personnel and lack of robust referral and follow-up systems.[5]

The gynecologic oncology MDT clinic integrates patient care into a single setting by assessing new and follow-up patients. All new patients are examined by oncology and gynecology physicians, and departments agree on a patient treatment plan. The clinic facilitates early review of new cancer cases by all necessary departments in the hospital as well as private facilities with the intention to educate patients about their diagnosis and treatment plan, decrease treatment delays as well as facilitate access to palliative care and social work interventions. Treatment and patient outcomes are reported during follow-up, which is crucial to identify disease recurrence/progression and establish appropriate patient management. The objective of post-treatment follow-up is to educate patients on late treatment side effects and how to manage them, and refer the patients if necessary to other specialists for intervention.[6,7] Since its conception in May 2015, the MDT clinic has seen over 1000 patients. However, during this period, in addition to poor physician-to-patient ratios,[8] challenges included incomplete hospital inventory of paper-based medical records,[5,9] fragmented communication between physicians and social work,[5] and patient loss to follow-up.[10] The barriers in structured communication resulted in no treatment initiation, delays in treatment, and/or inconsistent follow-up.[5-10]

A cross-sectional study surveying providers who used the application and patients enrolled via the application was conducted to assess the usability and effectiveness of OP Care.[11] The study found that 78% of providers did not feel OP Care increased their work burden and they were willing to use the application.[11] In addition, based on 19 questions regarding usability, providers stated they were very comfortable using OP Care.[11] Patients felt SMS reminders were very helpful, but preferred messages in Setswana instead of in English.[11] Further, attendance of scheduled new patient appointments has increased from 45% to 60% in just over a year since implementing OP Care and patient reminders. We will continue to follow OP Care data for new patients and follow up on patients over time as the OP Care application continues to be modified to further improve patient follow-up and retention rates. In the long term, we also plan to study reduction in patient delays and improvement in patient outcomes as a result of OP Care implementation. Thus far, we believe the integration of OP Care into the clinic has improved access to medical records, clinic schedules, and patient follow-up, allowing the healthcare workers to focus on patient

management and treatment counseling. The healthcare team can spend more time on patient care instead of worrying about obtaining medical records and managing the schedule.[11]

Despite the SMS reminders, several appointments were missed. Although there are no data from the MDT clinic on reasons for missed appointments, a recent study in Botswana evaluated reasons for missed appointments. In a cohort of 488 patients, 172 missed appointments due to work obligation, family duties, transportation fees, and forgetting the appointment date.[12] While OP Care will not be able to improve missed appointments due to work and family obligations, we hypothesize that SMS reminders will decrease missed appointments from forgotten appointment dates. In addition, due to poor death registration, some patients lost to treatment may have died. OP Care will add questions for reason of missed appointments to help develop problem-specific interventions.

CONCLUSION

The use of OP Care in a LMIC gynecology oncology clinic setting demonstrates the feasibility and efficacy of user-friendly mobile technology to improve patient record storage, treatment monitoring, appointment scheduling and tracking as well as patient compliance with booked appointments. In addition, real-time data output enables personnel of varying skill to assess clinic data, providing a simple method for clinics to identify gaps and measure quality improvement. We plan to expand use of this application to other oncology clinics as well as other specialties. Future steps also include studying improvement in patient retention and outcomes as a result of an OP Care application.

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RADIATION ONCOLOGY CASE

Complete response after treatment with pembrolizumab in a patient with metastatic cutaneous squamous cell carcinoma involving the cavernous sinus

Vamsi Varra, BS; Richard B. Ross, MD; Brian Gastman, MD; Claudia M. Diaz-Montero, PhD; Jessica Geiger, MD; Shlomo A. Koyfman, MD

CASE SUMMARY

An 84-year-old man with a history of numerous nonmelanomatous skin cancers of the face presented with blurry vision and diplopia, as well as numbness and foreign body sensation to the right face. MRI demonstrated an enhancing mass encompassing the lateral rectus muscle in the right orbit, extending dorsally until the anterior cavernous sinus (**Figure 1A**). This prompted a biopsy of the right orbital mass, which revealed poorly differentiated squamous cell carcinoma, suggesting recurrence of a previously treated cutaneous squamous cell carcinoma (cSCC) of unknown location. The mass was confirmed on staging positron emission tomography/computed tomography (PET/CT) with no evidence of nodal or distant metastatic involvement. The patient declined surgical intervention and instead was initiated on pembrolizumab, 200 mg every 3 weeks for 2 years, without any additional adjuvant chemotherapy or radiation therapy. For the patient's convenience, pembrolizumab was chosen over nivolumab, which is dosed twice a week. At the patient's next follow-up visit, 2-and-a-half weeks after the first cycle, the patient noted improvement of his diplopia and complete resolution of associated pain. An MRI obtained 4 months after initiation of pembrolizumab demonstrated a near complete response of the mass. At the patient's most recent follow-up, 2 years after initiation of pembrolizumab therapy, the patient has maintained his near complete response on follow-up MRIs, with further resolution of his visual symptoms (**Figure 1B**). Throughout treatment, the

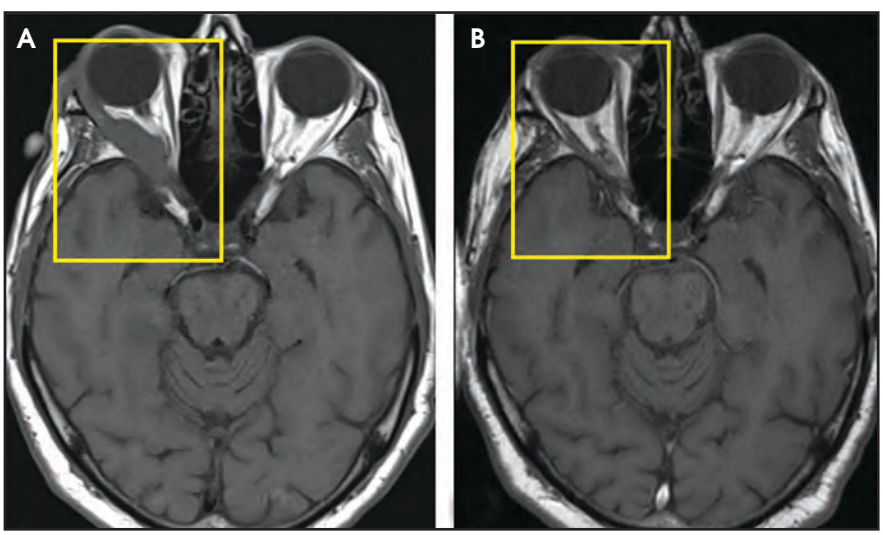

FIGURE 1. *MRIs demonstrating extent of tumor involvement before (1A) and after (1B) treatment with pembrolizumab in an 84-year-old man with cutaneous squamous cell carcinoma involving the right orbit extending along the cone of the orbit into the cavernous sinus.*

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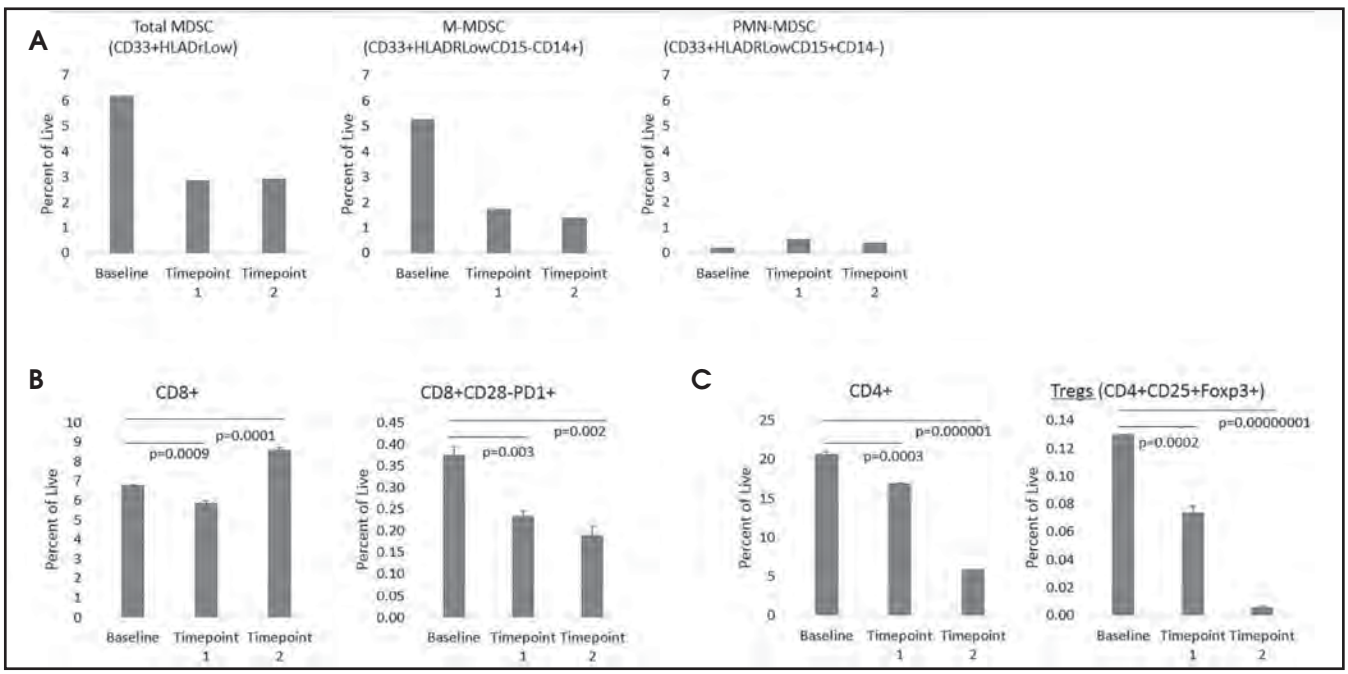

FIGURE 2. *Peripheral blood cells were isolated at the indicated time point, and levels of immune cell types were determined by flow cytometry analysis using the indicated markers. Levels are depicted as percentage of viable white cells. Significant changes in circulating levels were determined using the Student t test. Key: MDSC = myeloid-derived suppressor cells, M-MDSC = monocytic myeloid-derived suppressor cells, PMN-MDSC = polymorphonuclear myeloid-derived suppressor cells.*

patient experienced minimal toxicity, including hypothyroidism treated with replacement thyroid hormone.

IMAGING FINDINGS

Initial diagnostic MRI demonstrated an enhancing mass encompassing the right lateral rectus muscle extending posteriorly until the anterior cavernous sinus. A staging PET/CT scan demonstrated an F-18 fluorodeoxyglucose (FDG)-avid soft-tissue mass of the right orbit consistent with the mass seen on MRI as well as 2 FDG-avid cutaneous nodules in the left cheek and left posterior ear respectively, but no evidence of nodal or distant metastatic disease. The 2 cutaneous nodules, 1 of which was proven on biopsy to be basal cell carcinoma, were no longer noted on examination after completion of pembrolizumab therapy. During treatment with pembrolizumab, follow-up MRIs were obtained every 2 months for the first 6 months and then every 3 months afterward. These demonstrated continued near complete response of the cancer beginning 4 months after starting therapy.

DIAGNOSIS

Recurrent cutaneous squamous cell carcinoma of the right orbit involving the anterior cavernous sinus

DISCUSSION

PD-1 is a cell surface protein that sends a signal to dampen T-cell responses when activated. In cancer cells, PD-1 is often turned on with the goal of suppressing immune responses. Thus, preventing these molecules from interacting with their binding partners via antibody blockade can restore anti-tumor immune responses with significant clinical benefits.[1] Pembrolizumab, a monoclonal antibody targeting PD-1, has been shown to be efficacious in treating melanoma, lung cancer, mucosal head and neck cancer, gastric cancer, urothelial cancer, and triple-negative breast cancer.[1] In immunosuppressed populations, cSCC has a high mutational burden and has increased incidence. In other cancers, these attributes predict likely response to immunotherapy with a checkpoint inhibitor, prompting the investigation of PD1 inhibition as treatment for unresectable, locally advanced or metastatic cSCC.[2]

This patient's experience highlights the potential for PD-1 inhibition as definitive treatment of locally advanced or metastatic cutaneous squamous cell carcinoma, an entity typically treated with local resection and radiation therapy with or without concurrent chemotherapy. Our patient's clinical course is consistent with a previous case series that reported multiple complete and partial responses in patients with locally advanced or metastatic cSCC receiving anti-PD1 therapy.[1] Of note, a phase II trial elucidated the efficacy of cemiplimab, another PD1 inhibitor, in unresectable, locally advanced and metastatic cSCC.[2]

In addition, analysis of the patient's blood was performed, as part of an IRB-approved protocol, just prior to

treatment with pembrolizumab, and at 1 month and 10 months after initiation of treatment (**Figure 2**). A decrease in the levels of circulating myeloid-derived suppressor cells (MDSCs), particularly monocytic MDSCs was associated with response. The frequencies of circulating CD8+ T cells were slightly increased after treatment, whereas levels of circulating CD4+ T cells were significantly lower at the second time point measured. Interestingly, a significant reduction in the levels of suppressive CD8+ T cells (CD8+ CD28- PD1+) and regulatory T cells were also associated with treatment response.

The immunologic findings in this case are consistent with recent studies identifying changes in peripheral blood lymphocytes during treatment with immunotherapy. In this case, we observed a decrease in the peripheral blood levels of cell types associated with immune suppression such as MDSCs, CD8+ CD28- PD-1+ T cells, and regulatory T cells. Studies have demonstrated associations between both decreased MDSC levels and decreased regulatory T cell levels, respectively, with response to immune checkpoint inhibition in patients with melanoma.[3,4] Also, CD8+ CD28+ T cells were recently shown to be critical in anti-PD-1 therapy in lung cancer patients.[5] Therefore, decreased CD8+ CD28- T cell populations after treatment, which were observed in our patient's case, may be a marker of immunotherapy sensitivity in cSCC.

CONCLUSION

This report presents a case of a patient with recurrent, poorly differentiated cutaneous squamous cell carcinoma metastatic to the right orbit, tracking posteriorly into the cavernous sinus, causing blurry vision and diplopia. The patient declined surgical intervention and instead was initiated on pembrolizumab immunotherapy. After completing his regimen, the patient had a complete response to therapy, with resolution of his visual symptoms and stable appearance of the mass on follow-up MRIs.

Analysis of the patient's blood was performed prior to treatment, as well as at 2 time points afterward, and showed a decrease in various immune suppressive cell lines, such as circulating myeloid-derived suppressor cells, CD8+ CD28- PD-1+ T cells, and regulatory T cells. These cell lines have been associated with response to anti PD-1 therapy in melanoma and lung cancer, and as demonstrated by this case report, may be useful markers in response to immunotherapy in cutaneous squamous cell carcinoma as well.

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Strip alopecia in high-dose VMAT-based stereotactic radiosurgery

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CASE SUMMARY

Between 2013 and 2019, 298 patients were treated with stereotactic radiation therapy (SRT) and radiosurgery (SRS) techniques in our center. The dose fractionation schedules ranged from 30 Gy in 5 fractions to 30 Gy in 1 fraction. A mixture of centrally and peripherally located lesions was seen among the treated patients. Of these patients, 2 reported alopecia over the beam locus. One patient had been treated for arteriovenous malformation (AVM) with a dose of 25 Gy, and the other had been treated for brain metastasis with a dose of 22.5 Gy, both with single-fraction treatments. All plans were meticulously evaluated before treatment delivery. For the first patient, at the time of treatment planning, the scalp was not contoured and the scalp dose was not optimized, whereas for the second patient, drawing of the scalp and its optimization were carried out. On retrospective analysis of the treatment plans, the scalp was contoured on the first patient and its mean dose was found to be 637 cGy (25.5%) of the prescription dose; for the second patient, this was 593 cGy (26.4%).

The manifestation of alopecia in a conventional 1.8 to 2 Gy per fraction treatment regimen is seen with a dose of at least 25 to 30 Gy.[1,2] For single-fraction treatments, the typical dose is 5 to 8 Gy of biologically equivalent dose as per a conventional fractionation regimen.[3-5] Analysis of all SRS/SRT patients in our center shows a mean scalp dose of 429.0 ± 344 cGy. In our patient subset, we did not come across any incidence of alopecia in patients who received < 15 Gy in a single fraction.

Our experience points to the increased risk of permanent or temporary alopecia in patients having peripherally located lesions when the delivered dose to the planning target volume (PTV) exceeds 20 Gy. We recommended delineation of the scalp and including it in dose optimization.

Dr. Munshi *is the director of radiation oncology,* ***Dr. Sarkar*** *is a senior medical physicist,* ***Dr. Bansal*** *is an assistant consultant,* ***Dr. Rastogi*** *is a senior resident,* ***Dr. Ganesh*** *is the chief medical physicist, and* ***Dr. Mohanti*** *is a senior consultant, all at Manipal Hospitals, New Delhi, India.* ***Dr. Vaishya*** *is the director of neurosurgery, Fortis Memorial Research Institute, Gurgaon, Haryana, India.* *Disclosure: The authors have no conflicts of interest to disclose. 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.*

METHOD

We started our stereotactic program in 2013 and have presented results in multiple forums.[6-12] All patients were treated by a frameless stereotactic technique (SRS or SRT) using volumetric-modulated arc therapy (VMAT) on an Axesse (Elekta, Stockholm, Sweden) linear accelerator with a 4-mm multileaf collimator. Typically, SRS patients were treated by VMAT using 2 arcs (1 coplanar, 1 noncoplanar), and details of the planning strategy are presented in several studies.[6-13] In this report, we present the finding of 2 unusual cases of strip alopecia for cranial stereotaxy as shown in **Figures 1 and 2**. Further, to evaluate the dose-effect relationship, a scalp organ at risk (OAR) was drawn. The scalp was drawn on the ipsilateral side in all the axial slices in which the lesion was visible. Furthermore, the scalp was extended manually 3 cm in anterior, posterior, cranial and caudal directions. (This was checked by placing a dummy lateral beam ipsilaterally and seeing the projection of the PTV and the scalp in a digitally reconstructed radiography [DRR] mode). We considered only the

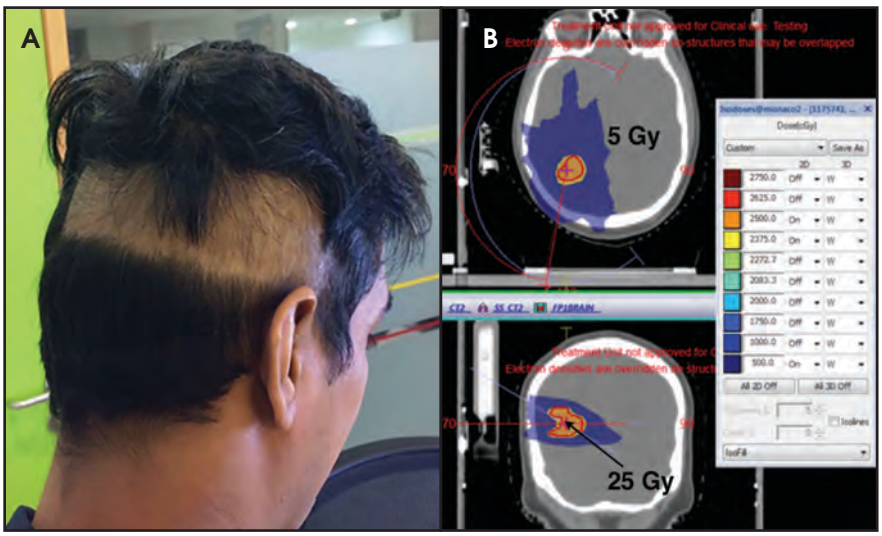

FIGURE 1. *Post-radiation therapy alopecia status for patient 1, who has arteriovenous malformation (AVM) of the right parieto-occipital region. He received 25 Gy in 1 fraction.*

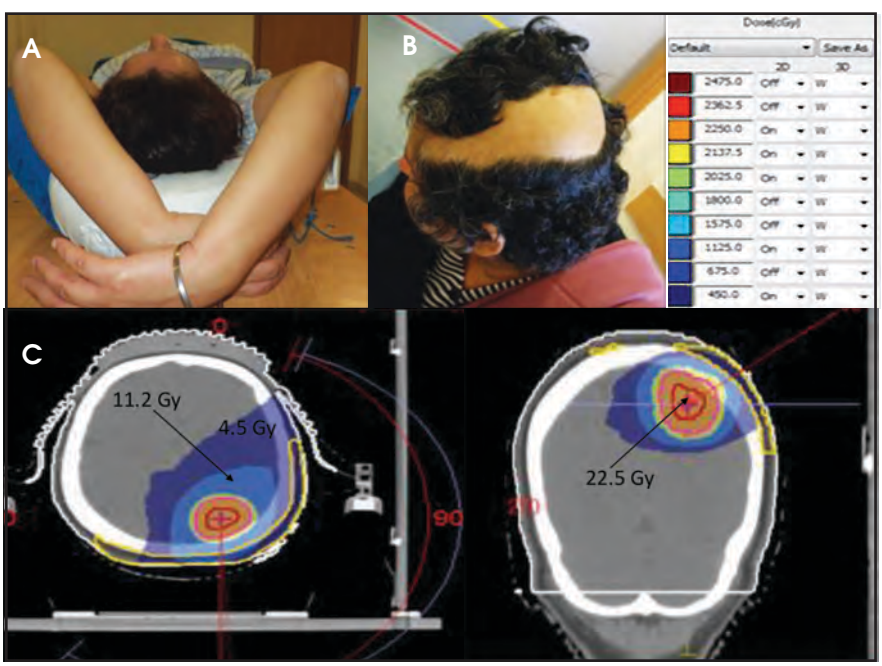

FIGURE 2. *Patient 2, who has a solitary brain metastasis from squamous cell carcinoma of the left lung, received 22.5 Gy in 1 fraction. Hair concentration before radiation therapy (A), alopecia status after radiation therapy (B). Radiation therapy planning and dose volume histogram (C). Blue indicates a 20% (4.5 Gy) isodose line.*

ipsilateral and partial scalp falling in the beam locus for optimization and dose evaluation.

Figure 3 presents the scalp as contoured in our clinic. No contouring guidelines are available for contouring the scalp. For the purpose of this study, the scalp was drawn as tissue between the outermost visible soft tissue (on the outside) and the bone/soft tissue interface on the inner side.

IMAGING FINDINGS

Figures 1 and 2 show an alopecia strip following SRS of the patients along with the dose-volume parameters of the radiation therapy plan. Both patients reported with strip alopecia after 2 months of their radiation therapy treatment. Two-year follow-up for case 1 revealed temporary alopecia with partial hair recovery. Initial evaluation of case 2 indicated permanent alopecia; follow-up data was not available as we lost contact with this patient.

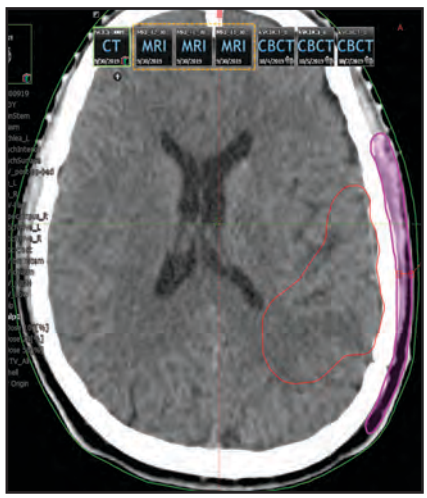

FIGURE 3. *Scalp is drawn as tissue between the body periphery and skull bone. First the "scalp" was drawn encompassing the body contour. Body contours are usually the thermoplastic mask. Further scalp was withdrawn from the body by 2 mm, bringing the scalp to within the body surface.*

Case 1 **(Figure 1)** was a 33-year-old man with AVM of the right parieto-occipital region. Digital-subtraction angiography showed a right 2.92 cm occipital nidus with extensive angiomatous changes. The patient received SRS treatment of 25 Gy in a single fraction.

Case 2 **(Figure 2)** was a 42-year-old woman with squamous cell carcinoma of the left lung. She received concurrent chemoradiation therapy followed by adjuvant chemotherapy. She developed solitary brain metastasis after a disease-free interval of 4 months, and treatment plans were made for a dose of 22.5 Gy in 1 fraction by SRS.

DIAGNOSIS

Case 1: AVM

Case 2: Brain metastasis

Table 1. Patient and Dose Characteristics

	Case 1	Case 2
Diagnosis	AVM right parieto-occipital region	Carcinoma left lung with solitary brain metastasis
Age	33 years	42 years
Sex	Male	Female
PTV volume	4.352 cc	14.496 cc
Arc start angle/arc length	190°/200°, 180°/40°, 190°/200°	20°/150°, 180°/40°, 180°/160°
Arc start stop resultant angle	380°, 360°, 380°	180°, 220°, 180°
Number of arcs used	2 coplanar partial, 1 noncoplanar	2 coplanar, 1 noncoplanar
Coplanar beams (Yes/No)	Yes	Yes
Prescription dose (PTV)/fraction	25 Gy/1 fraction	22.5 Gy/1 fraction
PTV dose maximum	2751.4 cGy	2792.9 cGy
Mean scalp dose	637 cGy (25.5%)	593 cGy (26.4%)
Smallest distance between facing edges of PTV and scalp	2 cm	1.8 cm

Key: PTV = planning target volume, AVM = arteriovenous malformation

Table 2. Analysis of Dose and Fractionation Regimen

Dose/Fraction	Average Prescription Dose (cGy)	Average Number of fractions	Average Dose (cGy)/Fraction	Cumulative Scalp Mean Dose (cGy)	Average Scalp Dose (cGy) / Fraction
≥ 15 Gy	2053.7 ± 385.9	1 ± 0	2053.7 ± 385.9	335.5 ± 179.3	335.5 ± 179.3
< 15 Gy	1754.3 ± 697.7	2.5 ± 1.8	918.5 ± 348.2	484.4 ± 406	188.5 ± 196.3

The table shows the average cumulative scalp dose and average scalp dose/fraction for 298 patients, with 41 receiving a dose/fraction ≥ 15 Gy and 257 receiving a dose/fraction < 15 Gy.

DISCUSSION

Over the years, SRS and SRT have become common practice in managing various benign and malignant brain conditions. The typical therapeutic doses are 12 to 30 Gy in 1 to 5 fractions. It is well-known that radiation therapy to the brain can lead to partial or total alopecia.[3] Several investigators have tried to prevent this by various techniques, with mixed results.[4,5]

As with all patients, the treatment plans involved stringent physics quality assurance testing before treatment to ensure dose accuracy. Both patients had a single lesion located peripherally (close to the skull) and were treated with a single fraction **(Table 1)**. In both cases, extensive alopecia was observed with complete loss of hair in the skull area corresponding to the paths of the treatment arcs. Our records of the 298 patients showed that alopecia was not observed in patients who had a centrally located lesion (eg, secretory pituitary adenoma cases treated with a single dose of 25 to 30 Gy). Similarly, when the prescription dose was < 15 Gy in a single fraction in both centrally and peripherally located lesions, the incidence of alopecia was not observed. The technique of determining a central vs peripheral tumor has been described in our early studies.[6] The analysis of dose and fractionation regimen as a function of dose/fraction ≥ 15 Gy and dose/fraction < 15 Gy is presented in **Table 2**. The total number of patients was 298, with 41 patients receiving a dose/fraction ≥ 15 Gy and 257 receiving a dose/fraction < 15 Gy. The average cumulative scalp dose for ≥ 15 Gy/fraction and < 15 Gy/fraction regimens is 335.5 ± 179.3 cGy and 484.4 ± 406 cGy, respectively, whereas the average scalp dose (cGy)/fraction remains the same for the former group and reduces to 188.5 ± 196.3 cGy in the latter group. Drawing of the scalp and dose optimization were performed for 35 out of 41 patients in the dose/fraction ≥ 15 Gy group, and 200 out of 257 patients in the dose/ fraction < 15 Gy group. The scalp was not drawn if the patient was already bald. About half of the patients were from different countries and we lost follow-up with a few of them. Inland

patients who received regular follow-up did not present with extensive strip alopecia other than these 2 cases.

After observing alopecia and its patterns, we contoured the partial scalp through which the beam entered with appropriate margins to determine whether any dose-effect relationship existed. The treatment planning data revealed that contoured strips of skull in the alopecia zone received a mean dose of 20 % of the prescription dose or less. The method section describes the technique of scalp drawing and its dose optimization. We drew a partial scalp since drawing a full scalp seems relatively infective in reducing dose to the relevant scalp area. The corresponding average absolute dose to the scalp was approximately 4 to 6 Gy for both patients. It is possible that actual surface doses were slightly different than doses estimated by the treatment planning system (TPS), but they are unlikely to be significantly higher. We did not perform in vivo dosimetry in our patients to confirm the TPS-estimated doses.

The phenomenon of alopecia observed in our cases is intriguing and surprising. VMAT arc-based treatment is an efficient technique of delivering treatment in a short span, causing the least patient discomfort. We used 2 noncoplanar arcs with large arc lengths, mainly aimed at increasing conformity and decreasing scalp dose. Despite these efforts, alopecia occurred. Our experience shows that one must be careful while treating peripherally located brain lesions with an SRS dose exceeding 20 Gy using a double-arc VMAT technique since there is an increased likelihood of hair loss even with the most meticulous planning and dose constraints to the scalp. The resultant alopecia is not patchy but continuous in nature and follows the VMAT arc pattern. A possible suggestion to avoid this strip alopecia is to use multiple smaller fields or to use a full arc (360 degrees) at the time of treatment planning. However, a standard solution for avoiding alopecia is not yet available.

CONCLUSION

We present two atypical cases of alopecia in patients treated with VMAT-based, single-fraction SRS for peripherally located tumors. All precautions should be taken to avoid alopecia for hypofractionated treatment—especially cranial stereotaxy—to avoid cosmetic disfigurement. Further study is required to establish the causal relationship between alopecia and dose/delivery technique.

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