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Review paper

Radiomics in radiooncology – Challenging the medical physicist

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ABSTRACT

Purpose: Noticing the fast growing translation of artificial intelligence (AI) technologies to medical image analysis this paper emphasizes the future role of the medical physicist in this evolving field. Specific challenges are addressed when implementing big data concepts with high-throughput image data processing like radiomics and machine learning in a radiooncology environment to support clinical decisions.
Methods: Based on the experience of our interdisciplinary radiomics working group, techniques for processing minable data, extracting radiomics features and associating this information with clinical, physical and biological data for the development of prediction models are described. A special emphasis was placed on the potential clinical significance of such an approach.
Results: Clinical studies demonstrate the role of radiomics analysis as an additional independent source of information with the potential to influence the radiooncology practice, i.e. to predict patient prognosis, treatment response and underlying genetic changes. Extending the radiomics approach to integrate imaging, clinical, genetic and dosimetric data ('panomics') challenges the medical physicist as member of the radiooncology team.
Conclusions: The new field of big data processing in radiooncology offers opportunities to support clinical decisions, to improve predicting treatment outcome and to stimulate fundamental research on radiation response both of tumor and normal tissue. The integration of physical data (e.g. treatment planning, dosimetric, image guidance data) demands an involvement of the medical physicist in the radiomics approach of radiooncology. To cope with this challenge national and international organizations for medical physics should organize more training opportunities in artificial intelligence technologies in radiooncology.

1. Introduction

Evolution of radiooncology towards an individualized patient treatment approach benefitted strongly from the increasing implementation of imaging technology in the radiotherapy process. From the beginning, medical physicists initiated and significantly contributed to this development. Aiming to integrate patient imaging in all phases of radiotherapy, medical physicists took over responsibilities in bridging over informatics and computer science with radiooncology. In this role, medical physicists were challenged to look more and more beyond the borders of their domains in dosimetry, treatment planning and delivery, quality assurance and radiation protection. In the attempt to optimize the treatment for each individual patient, yet long before the flag of *personalized medicine* was raised, medical physicists contributed most significantly by incorporating individual patient image data into the treatment process. Two major breakthroughs in this development can be identified so far: (i) CT-based treatment planning and (ii) image guided radiation therapy (IGRT) [1].

Following the adjustment of anatomical cross sections from standard atlases, shortly after the invention of computer tomography (CT) with its revolutionary role in radiology, the first step in the individualization of radiotherapy was the introduction of CT-based treatment planning [2]. Meanwhile, CT-based treatment planning has expanded towards multimodality-based treatment planning by

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integrating other imaging modalities, such as Magnetic Resonance Imaging (MRI) and/or Positron Emission Tomography (PET), aiming to further improve the definition of target volumes and critical organs [3].

Another breakthrough in the integration of imaging into the radiotherapy process was the image control of the treatment delivery at the treatment unit, known as IGRT [1]. From the beginning with the verification of the patient set-up on the treatment couch with film, up to the most recent technology of combined MR-linac systems, medical physicists were increasingly driving the integration of imaging into radiotherapy [4].

Now, we are facing a fascinating new field, so to say as the third breakthrough, where however medical physicists are not widely engaged yet, but certainly have to find their role in the future: quantitative image analysis or in short "radiomics" [5,6]. Radiomics can be considered a two-step process with (1) extraction of relevant static and dynamic imaging features, and (2) incorporating these features into a mathematical model to predict treatment outcome as discussed in the following subsections [7]. Radiomics is designed to assist the radiooncologist in the decision on the individual treatment of a patient, and to assess prediction and prognosis of the disease.

In institutions dealing with radiomics techniques, it is most important to establish an interdisciplinary team where medical physicists interact closely with clinicians, computer scientists and biologists. Applying quantitative image analysis combined with specific radiotherapy data as an individual radiooncomics signature for each treated patient requires fundamental knowledge of AI techniques, big data processing, medical imaging analysis methods, and the clinical and molecular biological basics relevant for performing radiomics and radiogenomics studies.

Mainly from the medical physicists view, this review addresses four questions: what radiomics is about, what are the methods used, what is the impact expected for radiooncology, and what is the particular challenge to medical physicists.

2. Radiomics in radiooncology – goals and workflow

Radiomics is a higher order data-driven concept, which initially has been used in radiology to support the detection of abnormal findings in the large sets of CT data. Due to modern computer technology in conjunction with efficient data mining, it became possible to extract large amounts of imaging features which associated with medical, biological and physical information may be clinically relevant, for instance for prediction of treatment outcome [8–10]. The previous mainly qualitative interpretation of images is now complemented by quantitative image analysis based on techniques of artificial intelligence (AI), including ML techniques such as deep learning (DL).

Expanding the radiomics concept to include molecular biology data (e.g. genomic, proteomic, metabolomic), also designated "radiogenomics", has broken new ground to generally characterize diseases, identify genetic variations and to predict treatment response by evaluating multidimensional imaging feature signatures. Translation of radiomics to radiooncology has been investigated with encouraging results over the recent years. An interesting aspect has been emphasized by authors from the QUANTEC group (Quantitative Analyses of Normal Tissue Effects in the Clinic) expecting more valid predictors for clinical outcome when combining traditional dose-volume quantities, endogenous biological biomarkers and radiomics features [11–13]. As proposed recently, an even more comprehensive collection of input data for radiooncology information analysis may be considered [11,14]. Such a "pan-omics" or "radio-oncomics" concept may for instance integrate all diagnostic and treatment data, specifically treatment planning images, image based 3D-/4D dose distribution, treatment verification and image-guidance data.

To implement the radiomics concept in radiooncology, it is recommended to establish a special interdisciplinary working group, which covers the related clinical, biological, physical, mathematical

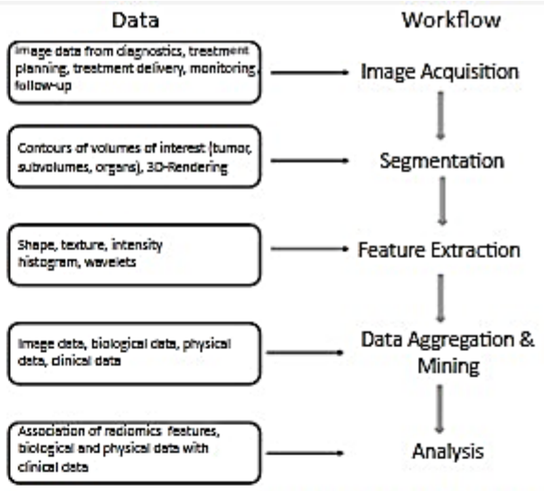

Fig. 1. Workflow of the radiomics concept in radiooncology.

and most importantly computer science skills. In order to assure an effective interaction and critical evaluation of the results, all members of such a group should at least have some fundamental knowledge on each mutual field of expertise. A typical radiomics workflow in clinical practice comprises the data acquisition, data processing and clinical testing of radiomics signature (Fig. 1).

3. Radiomics concepts and methods

3.1. Image acquisition, reconstruction, segmentation

Different modalities (CT, MRI, PET) have been explored as a potential basis for radiomics, where the choice of modality mostly hinges on the region of interest. In lung as well as head and neck cancer for example, CT (and PET) scans are considered standard of care, and most studies in these areas therefore focus on these modalities [15,16]. In gliomas on the other hand, MRI is dominantly used. A challenge in MR-based radiomics remains that the typically obtained anatomic MR images rely on visual interpretation of tissue contrast resulting from experimental pulse sequence parameters, and do not directly measure the underlying tissue properties. Recent advances in the field of quantitative MR imaging however have enabled to directly quantify properties like T1 and T2 relaxation times [17]. In addition, extending MR imaging beyond pure visualization of anatomy has further benefitted the field of radiomics. By visualizing key oncogenic features, such as angiogenesis or hypoxia, MR sequences, like diffusion or perfusion imaging, capture oncogenic processes and make them available for radiomics. In parallel, post-processing techniques have matured to a point where derived metrics, such as cerebral blood volume (from perfusion imaging) and tensor indices (from diffusion imaging) can be reliably assessed [18,19].

For most modalities and diseases, (semi-)automatic segmentation algorithms have been developed to supersede the time-consuming and often unreliable process of manual segmentation, as segmentation quality is critical for the subsequent analyses. In many fields, challenges have been designed to compare and benchmark these algorithms against each other, such as the Liver Tumor Segmentation Challenge (http://www.lits-challenge.com) or the Brain Tumor Segmentation Challenge (http://braintumorsegmentation.org). Furthermore, such a central evaluation of algorithms enables the synthesis of "meta-algorithms", which consider and weigh segmentation information from multiple algorithms to synthesize a substantially improved final segmentation. Such approaches may encompass simple strategies, such as majority voting or more complex algorithms such as STAPLE (Simultaneous truth and performance level estimation) [20,21].

3.2. Radiomic feature extraction

After image acquisition and segmentation, typically a set of image descriptors is calculated within the segmented volume of interest, which is then forwarded as input for ML models. Traditionally, simple intensity statistics (such as mean or standard deviation) or histogram parameters like kurtosis, skewness or entropy are used to characterize segmented regions of interest [22]. While these measures are straightforward to implement and computationally inexpensive, they are neglecting spatial information and are partially sensitive to normalization. For these reasons, modern radiomic approaches usually rely on more sophisticated image descriptors.

Image filters may be used to emphasize characteristics found in images, and can for example highlight edges. Typical examples of such filters include a median, Sobel or Scharr filter, which perform a filtering operation within a defined nxn neighborhood. Approaches that are more complex combine several filters, like the Laplacian of Gaussians (LoG), where first the image is smoothened using a Gaussian kernel and the Laplacian is calculated on the resulting image, highlighting regions of rapid intensity change.

Texture descriptors conceptually advance the above-mentioned metrics by incorporating spatial information. In the 1970s, Haralick et al. postulated a group of metrics calculated from a gray-level co-occurrence matrix to be used as image descriptors [23]. Haralick texture features are still in good use today, although they are also partially sensitive to normalization and are not (fully) rotationally invariant. To overcome these limitations, several strategies, such as wavelets or space-frequency representations have been proposed. Another approach are three-dimensional extensions of popular modern texture features, such as Local Binary Patterns (LBP) [24]. These texture descriptors overcome many of the aforementioned limitations, as they are rotationally invariant, insensitive to normalization and encode spatial information. However, these features are computationally expensive, and usually require elaborate post-processing strategies to generate meaningful image region descriptors. Nonetheless, the advantages of these texture features are leading to their more widespread use today.

Given the popularity of DL (see below), unsupervised learning methods have also been used to generate texture descriptors. A prominent example is the Auto-Encoder, an unsupervised deep neural network. Using a stacked architecture of convolutional, activation and pooling layers, the input image is reduced to a feature vector. Next, the decoder part maps the feature vector back to the input image space. The filters in the convolutional layers of the auto-encoder architecture are learned through backpropagation of the reconstruction error, defined between the original image and the reconstructed image.

Besides features derived from intensities, shape features are commonly used in radiomics. Given a proper input segmentation, descriptors of shape, such as sphericity or surface-volume-ratio, can be easily computed from 2D and 3D images. Given that shape features encode information complementary to intensity information, both feature categories are usually used in parallel. To facilitate their use, several open source packages implementing shape features are available, with PyRadiomics being one popular example (http://pyradiomics.readthedocs.io) [25]. Multiple publications have discussed the influence of different radiomic software implementations on numerical feature values [6,26]. To harmonize the use of radiomics, the image biomarker standardization initiative (IBSI) created a dictionary of standardized mathematical definitions of radiomics features [27]. Despite this harmonization of mathematical equations the software implementation itself appears to have large impact on numerical feature values and thus the prognostic relevance of radiomic features [26]. To compensate this, Lambin et al. proposed a comprehensive reporting system for radiomic studies with the aim to facilitate reproducibility [6]. A digital phantom was published online that can be used as a basis to calculate numerical feature values with the respective radiomic software. Integrating this data into scientific publications would improve comparability for other researchers.

3.3. Prediction models – the need for machine learning

ML has increasingly been established as one of the most essential tools in molecular biology ever since its breakthrough in protein structure prediction [28]. ML is one of many terms describing algorithms that learn from and make predictions on data. With the explosion of data, this technology has now evolved as the major solution for problems from playing games like Go and chess to improving the interaction between user and operating systems. Mostly used are methods referred to as *Artificial Neural Networks* (ANN; originally meant to model brain functions), *Random Forests* (RF), or *Support Vector Machines* (SVM) [29–31]. These and others have been applied to problems in radiomics [32–35]. The latest breakthroughs are made available through very powerful computing units (so called GPUs) in combination with massive amounts of data. These are referred to as *DL* methods (e.g. Deep *Convolutional Neural Networks*, CNN, or restricted Boltzmann machines). They have succeeded in voice and image recognition, and have recently also intruded into classification and segmentation tasks relevant to radiomics [36,37]. Furthermore, they have been demonstrated to boost the performance in protein structure prediction [38]. The deep CNNs can learn manifold more complex relations between input (e.g. image) and output (e.g. diagnosis or classification) than traditional ANNs. Of note, these techniques do not require the input of pre-calculated image features as described above, but rather learn these features "on the go", as usually whole image volumes are fed into these models. The main difference between convolutional layers and fully-connected layers is that convolutional layers treat the spatial structure (e.g. 1D, 2D, or 3D) of their input in a very specific way. In addition to the spatial dimensions, the data also has channels (i.e. voxelwise features). There is one property of input data and two properties of the desired input-output mapping which characterize the appropriate use of a convolutional layer: A convolutional layer provides so-called *spatial shift-equivariance* (i.e. if the input is shifted in space then the output is shifted in the same way) and *spatial locality* (i.e. an output pixel is influenced only by input pixel values that are not far away in space) of feature extraction for so-called *regular-grid data* (i.e. data with a uniform spatial neighborhood structure). These properties are implemented in convolutional layers in the following specific way. Convolutional layers train filters which perform a "multi-channel version" of discrete convolution. These filters can be understood to be small fully-connected layers themselves that operate equally on each local image patch. For example, one such filter might take a 5×5 pixel patch (all its channels) as the input and produce one output pixel (one filter for producing each output channel). The filter slides over the whole image producing the output values arranged in space. Since the same filter is applied to all patches of the image, useful low-level features (e.g. image intensity patterns) in early network layers, or complex features (e.g. tumors) in deep network layers (composed from the detected low-level features from previous layers) can be detected regardless of their location. Multiple such filters can be trained to recognize several different types of low-level structures and their outputs combined in the next layer.

Besides the supervised learning algorithms mentioned above, there are also unsupervised algorithms. Unsupervised means that they are applied to unlabeled data, i.e. the patients are not categorized in any way. Such algorithms try to find recurring patterns in the feature space and cluster the observations (patients) by similarity. The resulting groups could then be analyzed for common traits, e.g. duration or chance of survival.

3.4. Challenges of ML

The price to pay is that they require manifold more what the ML field refers to as labeled data, namely examples for which the correct map from input to output is known. So, to really profit from the power

of deep CNNs in molecular and medical biology, larger amounts of data are needed, and in particular labeled data.

Modern image analysis pipelines can easily yield a large number of image features, readily approaching the complexity seen in genomics [25]. Such amounts cannot be processed and interpreted by hand. Thus, computer-assisted methods like ML are crucial to fully utilize all the available data.

Due to the complexity of the problems that it tries to solve, ML often requires substantial expertise. The major challenge lies in the simple reality that ML extracts the true map between input and output correctly if and only if the data has been prepared adequately. What works in many fields in which ML has been succeeding often fails in biology [39,40]. To over-state the problem in a paradox: you need to fully understand your data before you can blindly apply ML to understanding it. Failing to understand the data will produce wrong models. In the best case, performance will be dismal. As long as the user is aware of that problem it might not be one. One example often causing problems in radiomics are unbalanced data sets in which one outcome (or class) is strongly over-represented (e.g. most patients die or disappear, for very few healing is consistently tracked over long periods). If not properly accounted for, such an imbalance will induce a strong bias in the decision process toward the class which is over-represented in the training set. Over- or under-sampling some of the classes might correct for some of the imbalance.

3.5. The need for feature reduction

Arguably worse than not obtaining an impressive performance is when developers over-estimate performance. Typically, this happens because the ML over-fits the known data: an extremely common trap. One reason could lie in redundant data. Having hundreds or thousands of features might not help if there are only few samples (patients) to train on. To avoid over-fitting, models typically need more samples (patients) than free parameters (features). Although the exact number depends on the variance in the dataset, a rule-of-thumb is to have at least ten times more samples than free parameters. Selecting the most predictive features might become crucial to reduce the free parameters and eliminate redundant or not informative features. Multiple strategies for dimensionality reduction of the feature vector have been proposed, though exploring all of them would go beyond the scope of this work (see Parmar et al. or Leger et al. for a more detailed analysis [32,34]). Intra class correlation (ICC) tests the reproducibility of features by comparing annotations from multiple operators (physicians) and removes instable features. However, this increases the workload since at least parts of the data set must be annotated several times. Other methods, like minimum redundancy maximum relevance (mRMR), try to reduce the feature space by removing inter-correlated features while retaining those highly correlated with the endpoint. Thus, noisy features (low correlation with the endpoint) are eliminated and the feature space is further reduced by only keeping a single feature out of every group of correlated features. Finally, some methods simply sample part of the feature space (forward or backward selection, hill climbing, genetic algorithms) and compare the overall performance of those subspaces until a stop criterion is fulfilled, e.g. the improvement is less than a certain threshold. However, any endpoint-specific feature selection, i.e. whose method takes the endpoint into account, must never be applied to the whole data set, but for example within cross-validation. Otherwise, the selected features and the final model can be heavily biased. On the other hand, one advantage of some modern ML algorithms (e.g. RF) is their ability to analyze a high-dimensional data set without prior selection of "candidate features", by automatically weighing each feature, and hence leverage the full information contained in the data set.

3.6. Validation of ML models

ML models must be rigorously validated. A model's predictive performance should never be evaluated on the same data on which it was developed. Testing the model on another cohort, ideally one that became available after the method development, would be preferable, but is not always an option. If an external validation cohort is unavailable, the easiest solution is to first split the data into two parts (e.g. 70% and 30%), train on the first part, and test on the second. However, if the data set is already quite small (less than 100 patients), splitting it in this way further propagates the problem of insufficient training and test data. Three common solutions to this approach are cross-validation, leave-one-out, and bootstrapping [41].

In k-fold cross-validation the data is randomly split into k parts (folds) of equal size. All but one of those folds is then used to train the model and the last fold to test its performance. This is repeated k times, each time changing which folds are used to train and validate, until the model has been validated on each fold exactly once. Thus, the final performance estimate includes all data points instead of only a certain percentage. If the ML model includes hyperparameters, those must be optimized on the training data only. To avoid overfitting nested cross-validation should be applied, i.e. the training data is again split into parts and each part is used for parameter optimization once. Leave-on-out, or jackknife, is a special case of cross-validation in which the number of folds is equal to the number of data points. Thus, during each iteration the model is trained on all but one data point and validated on the one left out.

Bootstrapping artificially increases the amount of data by creating new data sets of equal size randomly sampled from the original one. As the sampling includes replacement, some data points can be included in the new data sets multiple times while others are left out. The model is then trained on those data sets and validated on the data points not included in the random sample. This process can be repeated an arbitrary amount of times (often 100–1000 times) yielding a distribution to estimate confidence intervals of the true performance. If retraining the model is too computationally expensive to repeat it hundreds of times, predicting the data only once (e.g. cross-validation) and resampling the predicted data can also help to generate confidence intervals.

4. Impact of radiomics on radiooncology

4.1. The potential and limits – predicting individual patient risks and treatment outcomes

Besides the technical details of the radiomics workflow described above, the clinical endpoint is fundamental to generate meaningful results. Generally, radiomics has been for prognostic assessment of patient outcome and prediction of therapy response.

Many studies have applied radiomics to generate models predicting patients' survival. A complex endpoint as survival, however, does not only depend on tumor properties, but to a great extent on patient-specific details, such as age, gender or performance index [42]. A radiomics classifier always needs to be compared to such known existing prognostic factors to prove its incremental value. For optimal model performance, a combination of radiomics and clinical factors may be necessary as described below. For a better estimation of the value of tumor-specific radiomic signatures, the disease-specific survival may be a more accurate endpoint. Disease-specific survival endpoints were successfully applied for several entities such as glioma or colorectal carcinoma [43,44]. Further prognostic endpoints include local and systemic progression free survival quantifying the individual risk of recurrence. Both could be directly translated into clinical adaption of therapy regiments by escalation of local or systemic therapy modalities.

Finding an appropriate endpoint to assess therapy response constitutes a more challenging task. Some studies have chosen post-

therapeutic well-proven prognostic factors, such as the pathologic complete response in rectal cancer [45]. However, for other malignant entities, as shown for soft tissue sarcomas, the same endpoint may not be adequate [46]. Alternatively, the radiomics classifier itself could be generated post-therapeutically and used for predictive assessment [26,47]. Apart from absolute radiomics features, "delta radiomics" representing the absolute or relative change of features can be calculated quantifying the therapy-dependent changes of features [48]. Alternatively, the concept of "radiogenomics", correlating radiomics with underlying genetic changes, could be applied to monitor therapy response by determining the expression of the oncogenes targeted by a given drug.

In first studies, radiomic analyses were performed on the basis of CT data. For patients with Non Small Cell Lung Cancer (NSCLC), multiple large retrospective trials demonstrated the prognostic potential of CT-based radiomic classifier predicting survival and systemic progression after radiotherapy (RT) [16,49]. A recent study demonstrated the feasibility of the radiogenomics concept by predicting the clinically relevant EGFR and KRAS mutational status with high accuracy, especially when combined with clinical information [50].

Multiple studies have investigated the value of radiomics in PET-imaging [51]. 18-Fluordeoxyglucose (FDG)-PET/CT was subjected to radiomic analysis showing predictive capabilities for survival, disease progression and pathological treatment response for multiple entities including esophageal cancer, NSCLC and head and neck cancers [52–54]. Besides FDG, amino acid-based PET imaging plays an increasing role in daily clinical practice. Textural features of 18F-fluoroethyl-l-tyrosine (FET)-PET outperformed standard measures differentiating WHO grade III and grade IV gliomas, and predicting overall survival (OS) and progression free survival (PFS) [55].

Nowadays, MRI plays a key role for diagnosis, follow-up and treatment planning for many malignancies. Functional imaging, such as diffusion- or perfusion-weighted sequences has greatly enhanced clinical applications. Radiomics has the potential to advance MRI analysis one step further. Exemplarily, for prostate carcinoma patients, MRI-based radiomics may be used for Gleason score determination and distinction of carcinoma from benign tissue as an alternative to invasive biopsies [56,57].

In patients with Glioblastoma Multiforme (GBM), MRI-based features were shown to predict OS and PFS [58–64]. Notably, radiomics-based prognostic models inherit an additional value beyond clinical, molecular and standard as well as functional imaging parameters [42,65]. Further on, multiple studies demonstrated significant correlations with distinct gene expression profiles [63,66]. In particular, imaging features significantly correlated with prognostic relevant molecular GBM subgroups [58]. For instance, simple volumetric measures of GBM compartments such as the volume ratio of T2 hyperintensity to contrast enhancement and central necrosis showed significant prediction of the prognostic relevant mesenchymal GBM subtype with an AUC of 0.93 [67]. In a distinct study, the feature minimum histogram intensity of GBM Edema was correlated with the mesenchymal GBM subgroups. The group was also able to link quantitative imaging features to driver-gene dependent transcriptional programs [63]. Mutational status of oncogenes were predicted by radiomics features, too [68]. Promoter methylation of O(6)-methylguanine-DNA methyltransferase (MGMT) constitute a favorable prognostic factor for patients receiving temozolomide-based chemotherapy [69]. A recently published multiparametric MRI-based radiomic signature achieved an accuracy of 80% in predicting MGMT promotor methylation status in an independent validation cohort [70]. At the same time, histogram and textural features of multiparametric MRI enabled an automatized grading system for gliomas differentiating WHO grades I-IV with an accuracy of 0.961 [71]. Apart from these feature extraction-based models, DL techniques, such as CNNs supplied with sufficiently large patient cohorts, may improve performance in the future. First studies showed promising results with an accuracy of up to 0.899 in differentiating short and long time survival obtained in a cross-validation cohort [36,72].

Despite radiomics' great potential, novel classifiers need to prove their clinical usefulness by means of statistical calibration, discrimination and finally validation in independent patient cohorts. In addition, radiomic models should inherit an incremental value above existing models. Exemplarily, simple clinical parameters outweighed diffusion- and perfusion-derived MRI parameters for survival prediction in GBM patients making its clinical application unnecessary [73]. On the other hand, several studies underlined that the combination of radiomics signatures with clinical, molecular and established imaging parameters yielded the highest model performances [42,50,65].

4.2. Enhancing efficiency by tumor habitat targeting – the radiomic target volume

Independently of risk prediction, target volume definition may be significantly enhanced by quantitative imaging information during initial treatment planning. Today, volumes are defined based on CT, MRI and/or additional functional imaging information such as PET. By including information extracted from radiomics analyses, subvolumes might be identified, that require higher (or lower) doses. This may enable sophisticated dose painting targeting a "radiomic target volume" (RTV) [74,75].

In contrast to manual segmentation, quantitative imaging features at the basis of (semi-) automatic segmentation may help to reduce interpersonal variability. In head and neck cancer patients, the principle was tested by training a decision tree-based K nearest neighbor classifier using multimodal PET/CT texture- and intensity-features. Each voxel was either classified as normal or abnormal yielding a high segmentation accuracy compared to expert contours from expert physicians [76]. Another group used a quantitative feature profile for tumor identification and automatic segmentation in prostate carcinoma patients. Further on, they followed the above-mentioned concept generating a focal boost to the RTV. The resulting dose distributions achieved a reduced dose to organs at risk demonstrating a potential benefit by applying radiomics-guided target definition [57]. For the segmentation of GBM, multiple supervised and unsupervised automated methods were developed such as the random forest classifier-based BraTumIA software [77,78]. Such software implementation achieved high consistencies with manual expert segmentation with dice similarity score (DSC) of up to 86% [79]. Moreover, there are ongoing efforts to train supervised neural networks for image segmentation in academics and industry [80]. A CNN-based approach yielded a high segmentation accuracy with a DSC of up to 92% in a training data set of malignant gliomas which was reproduced in the BRATS 2013 challenge dataset with a DSC of 88% outperforming competing models [81].

4.3. Adaption of treatment to individual patients

Treatment adaption constitutes the standard of care today and most advanced treatment machines offer online CT or MR-imaging. An "adaptive segmentation system" could use radiomics classifiers for tumor identification, as well as for measurement of intra-treatment tumor changes for direct therapy adaption. As a consequence, tumor subvolumes that do not respond to therapy could be identified as an intra-treatment RTV and directly treated with a sequential dose escalation (boost). This concept corresponds to computer aided detection (CAD) methods that have been applied to medicine since the 1980 and which constitute the basis for today's radiomic studies [82]. Such an "adaptive radiotherapy" tailoring the RT concept to the individual patient dependent on intrinsic tumor properties would be one of the implementations of "personalized medicine" in radiation oncology [83].

Nowadays, the most benefit of adaptive radiotherapy is present for tumors changing geometry rapidly during the course of treatment, e.g. head and neck tumors, lung cancer, or sarcomas; in some cases, not only

tumor response but also physiological changes of the patients, e.g. weight loss, can have significant impact on the treatment plan [84]. Following this novel concept, prognostic relevant spatial patterns obtained from intra-treatment CT, MRI or PET imaging studies could be used as the basis for adaption of RT concepts. For example, changes of radiomic features on intra-therapeutic diagnostic CTs obtained weekly during RT had prognostic relevance in NSCLC patients [47]. Early data showed that radiomics can also be meaningfully applied to image-guidance CTs, which might be an alternative for the adaptive radiotherapy workflow [85]. With online MR-imaging, which is now available in some centers, the full benefit of radiomics can be used due to better soft tissue resolution, functional imaging, "online imaging capabilities" and the lack of additional radiation dose by adding MRI [86]. In an exploratory analysis of intra-therapeutic diagnostic dynamic contrast enhanced MRIs of head and neck squamous cell carcinomas a RT-dependent change was shown [87]. In a comparable approach, histogram features of ADC maps of intra-therapeutic MRIs showed prognostic relevance in an univariate cox regression [88]. Intra-therapeutic therapy response assessment via PET imaging constitutes a further source for treatment individualization. For instance, FDG PET studies obtained in the second week of RT of NSCLC patients showed prognostic relevance [48]. In neuronal malignancies static or dynamic metabolic tumor activity obtained from amino acid PET imaging could be used for a coherent approach [55,89,90].

4.4. Radio-oncomics: tumor and normal tissue dose response

Beside pre-therapeutic prognostic assessment, radiomics has the potential to become a powerful tool in radiation oncology by predicting not only tumor response, but also RT-related toxicities to the normal tissue. To describe this radiation oncology-specific field the term "Radio-Oncomics" has been proposed [11].

Predicting of RT-related tumor response has been investigated in several articles. In patients with NSCLC; changes in radiomics feature values obtained from CBCTs alongside RT had prognostic relevance [91]. In a different approach with bladder cancer patients, a DL model and feature extraction-based models were applied to determine bladder carcinoma response to chemotherapy on post-therapeutic CT studies, achieving similar results as expert physician ratings [92]. For rectal cancer, a recently published MRI-based radiomic classifier was able to predict pathologic complete response (pCR) to neoadjuvant RT with excellent performance [45]. Following current guidelines, RT is followed by rectal resection. Patients with pCR, however, have a superior prognosis even when surgery is omitted [93]. Radiomics could identify these patients that would profit from an organ-preserving RT-only approach.

Avoidance of normal tissue toxicity constitutes an important issue in treatment plan optimization. For the prediction of such effects, the Normal Tissue Complication Probability (NTCP) has been introduced as a function of the irradiated volume and the delivered dose [94]. Radiomics may add a further factor to the equation by quantifying patient individual tissue properties. Multiple studies did show the potential of radiomics to predict unwanted effects to normal tissue. A study by Cunliffe et al. analyzed CT-based textural and intensity features from randomly selected regions of interest of the lung of pre- and post-RT CT scans and correlated this information radiation dose maps, as well as the development of radiation pneumonitis. The results identified 12 independent features that correlated significantly with the development of pneumonitis [95]. For breast cancer, Chen et al. observed an increase of mean intensity primarily in the inner parts of the breast, which correlated with breast pain [96]. For head and neck tumors, parotid gland volume reduction has been shown to correlate with xerostomia [97]. Analysis of pre-therapeutic CT-based texture features recently showed significant correlation with parotid shrinkage and direct correlations with resolving xerostomia and sticky saliva [98,99]. Predictive models for both side effects were significantly improved by adding pre-therapeutic texture information. In a recent study, a CT-based radiomics classifier achieved an accuracy of 0.70 in predicting sensorineural hearing loss of RT of head and neck carcinomas [100]. These studies indicate the potential of applying radiomics to toxicity prediction.

4.5. Improving diagnostics

Follow-up in radiooncology may be enhanced by quantitative imaging information. Following radiation therapy of GBM, radiation necrosis and pseudoprogression constitute clinically important differential diagnoses to GBM recurrence. Currently, 18F-FET-PET is used in clinical practice for differentiation. Texture features may further improve diagnostic performance. Kebir et al. could demonstrate the potential of differentiating pseudoprogression from tumor recurrence outperforming the maximum tumor-to-brain-ratio (TBR) in a small pilot study [101]. Lohman and colleagues could show that diagnostic accuracy of delineating radiation necrosis from tumor progression increased after adding static textural features or dynamic time activity curve data to the TBR [102]. Recently, Prasanna et al. introduced a novel radiomics feature termed "Co-occurrence of Local Anisotropic Gradient Orientations". The proposed feature applied to MRI data showed high accuracy in classifying necrosis from recurrence, outperforming common quantitative imaging features, such as Haralick or Gabor filters [103]. Recently, Zhang et al. created a multiparametric MRI-based ML radiomics classifier to differentiate necrosis from recurrence of brain metastases after radiosurgery with an AUC of 0.72 [104]. Similarly, a CT-based classifier outperformed six physicians that were blinded to the outcome detecting local lung cancer recurrences after stereotactic radiation therapy in a matched analyses of 45 patients. To conclude, these studies underlined the fundamental potential of radiomics as a novel tool to improve patient care [75].

4.6. Stratification in prospective trials

To advance radiomics to the next level, prospective clinical trials are crucial. By definition of relevant parameters inside of the radiomics workflow, the full potential could be evaluated.

In future prospective trials, the radiomic prognostic classifier could be used as a basis for pre-therapeutic patient selection to distinct patient cohorts. Moreover, prospective validation of novel radiomics applications, such as radiomics-guided target definition, dose adaptations or diagnostic improvements would pave the way for their clinical translation.

5. Challenges for the medical physicist

The progress in medical imaging has profoundly pushed the development of precision radiotherapy-techniques, such as 3D CRT, IMRT, IGRT, stereotactic radiotherapy (SRT), brachytherapy/interventional radiotherapy (IRT), and particle beam therapy. Multimodal imaging turned out to be the most significant advancement achieving an individualized treatment optimization [105]. The continuously improving imaging methods have enabled an even better visualisation of the patient anatomy, including the localisation, character, extent and molecular profile of the tumor and the organs at risk. With the mechanical integration of imaging units into the treatment unit, e.g. conebeam-CT (CBCT) attached to the linac gantry, robot-controlled imagers mounted at the treatment couch, or most recently combined MR-linac systems, the concept of direct IGRT has been introduced [106]. The adaption of patient set-up with respect to physical, anatomical and physiological changes for each treatment fraction has become possible. However, so far conventional image analysis in radiotherapy has been limited to few observables like contours, intensity maps, dose matrices and histograms. It is the new era of 'Big Data', cheap computer power and sophisticated mathematical tools, which – far beyond

traditional limits – now allow to model myriads of variables, and image and texture features simultaneously to establish patterns in data [107]. Several clinical studies (see section "impact of radiomics on radio-oncology") demonstrated the predictive potential of these patterns when associated with the clinical outcome.

Against this background, the introduction of big data technologies in radiooncology, which comprise image, physical, clinical and biological data, generates a variety of new tasks in clinical practice and research, challenging the medical physicist as a member of an interdisciplinary radiooncology team.

5.1. Treatment planning

In the radiomics era, the techniques of multimodality imaging, currently used for pre-treatment diagnostics and treatment planning to define a computerized 3D patient model, may be supplemented by novel tools based on quantitative imaging, e.g. segmentation of structures, determination of biological markers and extraction of relevant imaging features. As emphasized already over a decade ago [108], the IMRT-capability of modern linacs allows to tailor a non-uniform dose distribution to the biological heterogeneous tumor ('dose painting') and hence to complement the ICRU concept of volumes by a 'Biological Target Volume (BTV)' [109]. Radiomics techniques with its potential to map genetic signatures of normal and tumor tissue on imaging data may be used to more precisely describe such a BTV as an RTV. The procedure of defining volumes will be extended beyond just drawing contours on different image data sets. Yet, open questions refer to the identification of relevant radiomics biomarkers capturing tumor and normal tissue geno- and phenotypic characteristics. Several studies are dealing with the prediction of radiation toxicity effects by associating radiomics features with 3D-dose distribution [110]. When incorporating the large amount of radiomics data into treatment planning software tools it is necessary to effectively process the various image data sets. As soon as such approaches become part of the standard clinical workflow in radiation oncology, the traditional role of the medical physicist in quality assurance of imaging modalities used for treatment planning needs to be broadened to include radiomics modalities. This might be quite challenging while radiomics algorithms and concepts are still developing, but the medical physicist must ensure that all input data to treatment planning fulfills the required standards for overall patient safety. This includes also the integration of radiomics modalities into the overall end-to-end tests in radiation therapy. Other tasks refer to the influence of the various uncertainties associated with respect to the definition of tumor boundaries and its biological subvolumes due to characteristics and limitations of each oncological imaging technology. Correlation of the 3D-dose matrix with the various individual or fused image data sets represents another problem, in particular when considering the impact of organ motion artefacts and day-to-day variations in patient setting-up and potential changes in the biological subvolumes during the course of the treatment. Associating dose-volume-time metrics with radiomics signatures to explore its predictive potential on clinical outcome (TCP and NTCP) requires basic and clinical research. Here, it is primarily the medical physicist who understands the limitations and potential pitfalls when correlating the 3D dose matrix with radiomics data. For example, the 3D dose matrix depends on the employed dose calculation algorithm and the resolution of the calculation grid, and standardization of such parameters can be quite difficult in multi-centric trials which aim at evaluating the clinical impact of radiomics features for either treatment planning or outcome modeling.

5.2. Treatment delivery

In order to track shifts in patient positioning and tumor location intra- and interfractional verification of the treatment delivery by means of integrated or on-board imaging devices is going to be standard in precision radiotherapy. These multiple imaging data sets acquired for IGRT can be used to quantify deviations from the treatment plan. Imaging features and biomarkers can be extracted from the sequence of IGRT-image data sets and associated with pre-treatment and planning image data to assess time dependent radiation response effects throughout the treatment course. In this context, the Delta-Radiomics concept could be used to quantify treatment-dependent tumor changes [47,48]. Recently, a study on CBCT-radiomics demonstrated the potential of these image data for survival prediction [91]. Recently, an exploratory study first demonstrated the prognostic potential of radiomics on the basis of electronic portal imaging device images [111]. Furthermore, radiomics models based on IGRT-imaging data may support the medical decision on a response dependent adaption during the treatment course.

5.3. Dose distribution

Spatial and temporal dose distribution (e.g. time-dependent effects due to dose fractionation or dose rate (e.g. brachytherapy)), the actually delivered and accumulated dose distribution, dose-volume relationship (e.g. dose-volume-histogram (DVH)), and the radiation type are the most significant physical determinants of radiation response and clinical outcome. When combining these physical quantities with predictive radiomic parameters from diagnostic images and IGRT imaging data, prediction of treatment response and radiosensitivity of the various types of normal tissue could be improved. However, most critical is the impact of uncertainties of the dosimetry data on the radiomics models which limits the clinical application of such a comprehensive approach.

6. Conclusion

Introduction of computerized medical imaging technologies turned out to be a milestone on the way to translating the approach of personalized medicine in radiotherapy. The various imaging techniques available today initiated novel treatment methods (IMRT, IGRT, breathing adapted radio therapy (bART)), individualized treatment planning and stimulated innovations in equipment technology up to the recent advent of MR-linac. Along that path, quite often it was the medical physicist who significantly contributed to this advancement in radiotherapy. Nowadays, we are again facing a new era where AI-based quantitative imaging technologies have started to manifest in radio-oncology. As demonstrated in various clinical studies, this new field of big data, providing powerful tools for analyzing large collections of information, may offer opportunities to support clinical decisions on treatment design and adaption, to improve predictions of patients' treatment outcome and to enable a better stratification of patient cohorts in clinical trials. Furthermore, association of the large data set of diagnostic and therapy-related digital information with tumor and normal tissue geno- and phenotyping data may stimulate research in clinical and basic science in radiooncology. In order to continue in playing an important role in the radiooncology team, the medical physicist needs to catch up with the rapid development of this field of AI-techniques increasingly being applied in radiooncology. With the increasing importance of imaging in radiotherapy the majority of medical physicists are already rather familiar at least with the fundamentals of imaging technology. However, it might be worthwhile to consider adapting the education curricula to include more radiomics related topics. National and international associations for medical physics should cope with this trend and launch initiatives to provide appropriate training in this challenging field of AI technology applied in all radiation imaging and therapy disciplines, particularly in radio-oncology.

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Declarations of interest

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UNIVERSIDADE DE SÃO PAULO
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PÓS-GRADUAÇÃO EM CLÍNICA MÉDICA

Processo Seletivo 2019 – 1º Semestre

PROVA ESPECÍFICA - Tema: Exatas Aplicada à Saúde

Data: 09/11/2018 **Número de Inscrição: 00**

QUESTÕES

(As questões poderão ser respondidas em português, inglês ou espanhol)

The questions of this test were based on the following article:

Radiomics in radiooncology – Challenging the medical physicist
Peeken JC, Bernhofer M, Wiestler B et al. Phys Med. 2018 Apr;48:27-36. doi: 10.1016/j.ejmp.2018.03.012

Please read and write your responses:

1. According to the authors, which are the tasks of a medical physicist when planning a radiation therapy treatment? (2,0 pts)
2. Also, according to the text, how do you define “radiomics”? (2,0 pts)
3. What authors discussed about image features extraction? (2,0 pts)
4. Briefly, (up to 15 lines) describe the impact of radiomics on radiooncology (2,0 pts)
5. According authors’ view, what are the challenges of the medical physicist for treatment planning? (2,5 pts)

Gabarito: Prova de Inglês 2019- 10 semestre – Exatas aplicadas a saúde -PPG-CM

1. According to the authors, what are the tasks of a medical physicist when planning a radiation therapy treatment?

R. O papel do físico médico no auxílio do tratamento radioterápico inclui várias tarefas:

a- garantir a qualidade das imagens médicas;

b- verificar que a dose de radiação seja a mais adequada possível ao plano de tratamento proposto;

c- analisar as imagens médicas geradas para o planejamento terapêutico de maneira individualizada e direcionada as necessidades de cada paciente.

2. Also, according to the text, how do you define “radiomics”?

R. No texto, “radiomics”é definida como a técnica que extrai atributos de textura das imagens médicas, através de análises quantitativas e, posteriormente, estas informações são inseridas em modelos matemáticos preditores da resposta terapêutica.

3. What authors have discussed about image features extraction?

R. Os autores discutem como atributos de textura, avaliados quantitativamente, pode contribuir para o planejamento terapêutico e melhor seleção de pacientes. Neste contexto, são discutidos como otimizar a abordagem da análise textural, já que o número de atributos utilizáveis é extremamente elevado. Os autores sugerem uso de filtros de imagem, por exemplo, bem como a consolidação de alguns atributos como os melhores, a partir da análise de uma grande quantidade de dados.

4. Briefly, (up to 15 lines), describe the impacto f radiomics on radiooncology?

R. A radiômica tem sido pesquisada para que o planejamento terapêutico de um determinado indivíduo seja feito levando em conta suas características particulares, o que é conhecido como medicina personalizada. Isto se refletiria em diferentes níveis de atuação”melhor definição de dose terapêutica, melhoria nos diagnósticos das complicações associadas a radioterapia e até estratificação de risco para adequação de inserção em ensaios clínicos randomizados.

Por exemplo, a radiômica pode ser utilizada para tentar predizer a dose ideal para o tratamento de uma neoplasia, especificamente para aquele paciente, que tem um tumor com características avaliadas pela textura. Outro uso, por exemplo, seria a predição de toxicidade relacionada a radioterapia, nos tecidos normais, adjacente a lesão a ser tratada, de novo a partir de informações específicas dos atributos de textura.

5. According to “authors view”, what are the challenges of the medical physicist for treatment planning?

R. Os autores descrevem que o físico médico deve se manter atualizado em relação às técncias terapêuticas mais modernas, como IMRT, IGRT, SRT e, além disso, das possíveis interações entre a radiômica e as técnicas de radioterapia. Além disto, deve estar atento a participação em discussões multidisciplinares, que objetivam otimizar o tratamento e, no futuro, envolverão o uso de dados derivados de grande quantidade de pacientes (“big data”) e incorporação de modernas tecnologias oriundas do uso destes dados e da radiogenômica.

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PROVA ESPECÍFICA - Tema: Exatas Aplicada à Saúde

Data: 09/11/2018 **Número de Inscrição: 00**

Folha de Resposta 1

Processo Seletivo 2019 – 1º Semestre

PROVA ESPECÍFICA - Tema: Exatas Aplicada à Saúde

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Folha de Resposta 2

Processo Seletivo 2019 – 1º Semestre

PROVA ESPECÍFICA - Tema: Exatas Aplicada à Saúde

Data: 09/11/2018 **Número de Inscrição: 00**

Folha de Resposta 3

Processo Seletivo 2019 – 1º Semestre

PROVA ESPECÍFICA - Tema: Exatas Aplicada à Saúde

Data: 09/11/2018 **Número de Inscrição: 00**

Folha de Resposta 4