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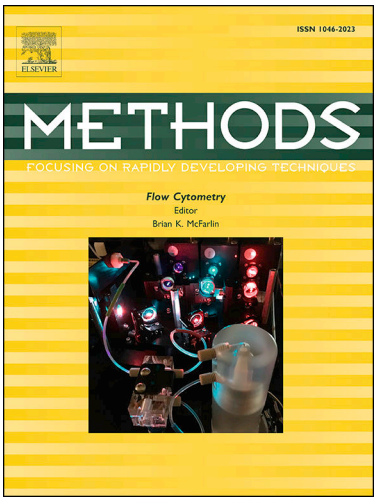

Reinventing Radiation Therapy with Machine Learning and Imaging Bio-markers (Radiomics): state-of-the-art, challenges and perspectives

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Highlights 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

- Radiation therapy harnesses numerous technological breakthroughs.
- Radiomics biomarkers from medical images become an asset for data-driven precision medicine.
- Promising applications of radiomics may add incremental value to patient care.
- Integration of these methods in clinics requires addressing technical caveats.

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Abstract

Radiation therapy is a pivotal cancer treatment that has significantly progressed over the last decade due to numerous technological breakthroughs. Imaging is now playing a critical role on deployment of the clinical workflow, both for treatment planning and treatment delivery. Machine-learning analysis of predefined features extracted from medical images, i.e. radiomics, has emerged as a promising clinical tool for a wide range of clinical problems addressing drug development, clinical diagnosis, treatment selection and implementation as well as prognosis. Radiomics denotes a paradigm shift redefining medical images as a quantitative asset for data-driven precision medicine.

The adoption of machine-learning in a clinical setting and in particular of radiomics features requires the selection of robust, representative and clinically interpretable biomarkers that are properly evaluated on a representative clinical data set. To be clinically relevant, radiomics must not only improve patients' management with great accuracy but also be reproducible and generalizable. Hence, this review explores the existing literature and exposes its potential technical caveats, such as the lack of quality control, standardization, sufficient sample size, type of data collection, and external validation.

Based upon the analysis of 165 original research studies based on PET, CT-scan, and MRI, this review provides an overview of new concepts, and hypotheses generating findings that should be validated. In particular, it describes evolving research trends to enhance several clinical tasks such as prognostication, treatment planning, response assessment, prediction of recurrence/relapse, and prediction of toxicity. Perspectives regarding the implementation of an AI-based radiotherapy workflow are presented.

Graphical abstract

See **Fig. 4**

Keywords maximum of 6 keywords

Machine-learning; Radiomics; Radiation Therapy; CT; PET; MR

Introduction

Radiation therapy (RT) is a pivotal cancer treatment used in about half of cancer patients.[1] RT can be used as a standalone option or in combination with other treatment strategies such as surgery or systemic therapies. Numerous technological innovations have substantially improved the radiotherapy landscape in the last decade. Beyond the rapid increase of computing capacities and the development of high conformal dose delivery systems, that have led to the advent of intensity-modulated radiation therapy, and stereotactic radiotherapy, the importance of imaging in radiotherapy has been steadily increasing both in terms of planning as well as in terms of treatment delivery.[1]

Patients' management in RT such as disease characterization, treatment planning, treatment delivery, and treatment follow-up rely massively on imaging technologies.[2] Computed tomography (CT) is the gold standard for dose calculations and the most common method for treatment implementation guiding patient repositioning and providing means for assessing the need of re-planning. Magnetic resonance imaging (MRI) is a radiation toxicity-free modality associated with better contrast in soft tissue regions. Its adoption is constantly increasing and is expected to acceleration with the arrival of commercial Magnetic resonance (MR)-Linacs. MR associated with multi-parametric imaging should allow improved target localization and motion management during radiation therapy for instance in lesions affected by respiratory motion[3, 4] while having the potential to drive dose adaptation and personalized dose escalation in a near future.[5] Positron emission tomography (PET) is the most prominent image modality to appraise tumor metabolism and achieve molecular imaging in clinical routine. 18F-fluorodeoxyglucose (FDG) PET images have been shown to help in target volume delineation thanks to their good tumor to healthy tissue signal ratio[6], even if they suffer from poor spatial resolution. Recent results from a clinical trial demonstrated that FDG PET-based dose planning allowed for a reduction in target volume and an improvement in local control in non-small-cell lung cancer patients.[7]

Artificial Intelligence (AI) is a broad term that encompasses different fields, such as machine learning and deep learning which is a subset of machine-learning. The term machine-learning defines algorithms, and mathematical models built to reproduce the relation between input-output for a given data set without necessarily following the principles of decision used to determine this relationship. Such models are often low dimensional and in general benefit from domain's information as it contains the most informative features. Deep learning algorithms are a subclass of machine learning that in general deploy high dimensional models that have an architecture close to neural networks which can be trained to predict an output without any explicit domain-related knowledge.[8] This review will focus on the more mature field of machine-learning analysis based on predefined features extracted from medical images, i.e. radiomics[9-11], although deep learning has the potential for a broad spectrum of applications.[12]

The recent and important adoption of radiomics illustrates a paradigm shift in RT.[13] Medical images used to be considered as pictures guiding an inherently subjective treatment planning. Radiomics is redefining medical images as a quantitative asset that can be used for decision support.[14-18] Radiomics derives from the quantitative transformation of images into comprehensive biomarkers, which are calculated automatically by algorithms using predefined mathematical formulas.[9-11] The added value of radiomics to optimize patient care could be threefold. First, radiomics is a noninvasive clinically relevant information space that is accessible / available at no additional cost. Second, radiomics when interpreted from algorithms is quantitative and tends to be reproducible, while the interpretation of medical images by physicians remains inherently subjective. Third, each step of patients' RT management can be divided into specific tasks, and AI technologies can be trained to excel in these narrow tasks so that clinicians across institutions can deliver the best reproducible treatment and save time for high value care.

Several tasks of the RT chain can take advantage of imaging biomarkers and associated machine-learning models. Today, conventional radiotherapy prescription is based on a "one dose fits all" concept with an objective of homogeneous dose delivery inside manually defined target volumes and identical dose-volume histogram constraints for every patient.[19] Machine-learning analysis of medical images has the potential to accelerate and improve reproducibility of target volume delineation.[20, 21] Future treatment decisions, including prescribed dose and compromise between organs-at-risk (OAR) sparing and target volumes coverage, will likely be guided by prognostic, response and toxicity models either directly at the beginning of the treatment or during the treatment using an adaptive strategy. In patients with brain, rectum or esophageal cancers, the evaluation of response to RT can be complex because of pseudo-progression and/or radiation-induced changes. Image analysis appears as an appealing non-invasive method to guide subsequent treatment strategies.[22, 23] Finally, the huge amount of retrospective data acquired at different treatment stages combined with increased knowledge about the correlation between image content, the sites of relapse/failure and underlying biology will surely guide targeted dose prescriptions also known as dose painting in the coming years.

Number of recent studies demonstrated that the adoption of radiomics and machine learning pave the way for improved patients' management in RT along with the fact that there is a great number of open technical issues related with their clinical adoption such as reproducibility, robustness and generalization. Hence, numerous technical caveats have to be considered [15-18, 24] and robust methodologies are needed to differentiate signal from noise in the medical images. This requires a standardization of image preprocessing, tissue segmentation, feature calculation, and statistical methodologies such as dimension reduction and feature selection.

In this review, we will first describe the current state of the art regarding radiomics pipeline implementation. We will then discuss how these technologies are currently used in clinical research to optimize the management of cancer patients treated with radiation therapy. Finally, this review will

focus on possible future implementations of radiomics in clinics. It should be noted there should be a clear separation between the notion of radiomics and the notion of artificial intelligence algorithms even though these two notions are interconnected within a clinical objective. Radiomics refers to a predefined set of imaging biomarkers while AI algorithms seek to determine a subset of them that once combined with a prediction mechanism are able to provide a prediction with respect to the considered clinical task.

Radiomics pipeline optimization: state-of-the art

Practices standardization

The use of radiomics-based biomarkers in a clinical context involves identifying and minimizing the impact of potential confounding factors on predictive models. Hence, the need for practices standardization for mainstream imaging modalities.

The capacity to replicate and validate radiomics studies is vital to produce sufficient and convincing scientific evidence for the translation of possible applications into clinical practice. The community needs to adopt consensual standards. A systematic review demonstrated that only 17% of radiomics studies addressed in detail every methodological aspect related to image acquisition, preprocessing, or feature extraction.[25] Another review showed that only 6% of radiomics studies fulfill rigorous requirements such as prospective validation in external datasets.[26]

Nonetheless, recent initiatives demonstrate a trend toward practices standardization. To bridge this gap, several efforts have been made to standardize the imaging protocols, including the Quantitative Imaging Biomarker Alliance (QIBA)[27], the Quantitative Imaging Network (QIN)[28], the Image Biomarker Standardisation Initiative (IBSI).[29, 30] The latest seeks to provide image biomarker nomenclature and definitions, benchmark data sets, and benchmark values to verify image processing and image biomarker calculations, as well as reporting guidelines, for high-throughput image analysis.

Finally, "FAIR (Findable, Accessible, Interoperable and Reusable) guiding principles"[31, 32], a brief enumeration of principles for better accessibility, interoperability and reusability of scientific data, should ease translation of radiomics into clinics.[33]

Data preprocessing and harmonization

The majority of radiomics studies use images extracted from standard of care clinical devices such as CT, MRI, and PET. These images are acquired with a wide range of scanning devices and manufacturers. The absence of standardized protocols leads to a significant variability in acquisition and reconstruction parameters. These parameters have been shown to affect the noise, the contrast and the spatial resolution of medical images impacting the subsequent measurement of shape, histogram, texture and higher-order features extracted from the images (see below).

CT

For CT images, several confounding variables can alter the estimation of imaging features such as acquisition and reconstruction parameters[34, 35], or quality of contrast-enhancement.[36-38] The impact of kernel filter, pixel size, slice thickness, kVp and tube current (mA) has been deeply investigated[39-43] and it has been demonstrated that reconstruction kernel filters (smooth and sharp) should not be used interchangeably.[40] Consistent spatial sampling is of fundamental importance

since it influences the measurement of a significant percentage of radiomics features[41], hence the interest of resampling all the image sets to a nominal voxel size.[42] In contrast, x-ray tube current is unlikely to have a large effect on radiomics features extracted from CT images of textured objects such as tumors.[43] Some studies suggested the use of convolutional neural networks for post-processing of retrospective data to improve radiomics reproducibility.[44] A simple solution would be to reduce variability by using predefined fixed CT parameters for image acquisition in future prospective radiomics studies.[45, 46]

PET

The conventional PET tracer in cancer imaging is 18F-FDG. Maximal Standard Uptake Value (SUV_{max}) is the mainstream imaging biomarker derived from the analysis of 18F-FDG PET images used to guide clinical decision.[47] Beyond SUV_{max}, new radiomics biomarkers are currently investigated. The reproducibility of these biomarkers is hampered by several factors, which can be either physiologic (i.e., blood glucose concentration) or technical (e.g. type of detectors and associated electronics, reconstruction algorithms).[48, 49] Harmonization guidelines have been formulated to ensure reproducibility of SUV in multicenter studies[50] and became concrete as early as in 2010 with the launch of the EANM/EARL accreditation program which seeks to standardize PET-quantification across centers for the use of the FDG PET as a quantitative imaging biomarker.[51, 52] Recent literature reviews addressed methods, pitfalls and challenges of radiomics analysis of PET images.[15, 53-56] Despite a low level of evidence for most of the 38 potentially-affecting factors, variations in acquisition type (static vs. dynamic), reconstruction parameters, voxel size and delineation seem to alter the extraction of radiomics features[53]. However, the majority of factors were shown to have a low impact on biomarkers reliability which was defined as the comparison between factor variability vs. inter subject variability. The authors recommended limiting deviations in reconstruction parameters including voxel size and the use of a unique segmentation algorithm and the same discretization scheme for the whole cohort till evidence level is increased.

MRI

A major caveat of MRI is that intensities are non-standardized and highly dependent on manufacturer, sequence type and acquisition parameters.[57, 58] Consequently, a large variability in intra-patient and inter-patient image intensities exists, and affects radiomics features.[58, 59] In order to solve this technical challenge, radiomics studies have adopted image pre-processing techniques. For example, it has been shown that bias field correction minimizes efficiently MR intensity inhomogeneity within a tissue region.[60-62] Spatial resampling can reduce the variability generated by different voxel sizes.[62-64] In brain studies, a brain extraction is mandatory in order to remove the skull that generates the most important variations in intensities[65, 66], and permits to define the

region in which intensities should be considered before any final image intensity normalization step.[62, 66]

Recently, radiomics studies have used a compensation method to pool cohorts from different centers. This data-driven post-processing method called ComBat [67] seems to be able to harmonize radiomics features a posteriori. Initially proposed to correct batch effects in genomic studies, it has demonstrated its effectiveness in PET [68] and CT imaging.[69, 70]

Tumor segmentation

In radiomics analysis, segmentation is a crucial step determining the region of interest for feature extraction and variability in contouring is known to alter the reproducibility of predictive models[71]. The absence of pathological gold standard in many clinical situations makes it difficult to evaluate the quality of the contours. Despite the well-known variability between readers, manual segmentation remains a standard in a majority of radiomics studies in RT.[72-76] The Intra-class Correlation Coefficient (ICC), that quantifies the intra- and inter-reader agreement, has been consistently used to evaluate radiomics features reproducibility.[77-79] Semi-automatic computer-aided segmentation approaches on top of addressing efficiency/saving time (manual delineation is time consuming) also improve the reproducibility in tumor delineation and feature extraction.[80-83] Recent advances in deep learning lead to the development of fully automatic segmentation methods [84, 85] using different architectures such as U-Net.[86] However, automatic segmentation is prone to errors, especially in the presence of artifacts, a poor signal-to-background ratio, noise and/or when the lesions of interest are very heterogeneous.[87]. In PET, guidelines are available about methods to use preferably depending on the clinical application. Conclusions showed that fixed thresholds should be avoided in realistic complex cases and are in favor on algorithms relying on advanced image analysis.[88] In CT and MRI, several studies highlight the benefit of using semi-automated or fully automated segmentation.[89-94] The main challenge refers to the definition of an optimal delineation itself. First, an optimal delineation could be defined by its ability to correctly reflect ground truth from a pathological point of view. However, ground truth is often defined by manual expert annotations in the context of radiomics. The performance of a segmentation tool could therefore be judged on its capacity to produce informative and reproducible features for the prediction of the outcome of interest, i.e., a given molecular or clinical parameter.

Grey-level discretization

The grey-level discretization clustering similar grey levels into bins for textural feature calculation has been proposed to minimize the noise impact and decrease calculation times.[95] This

additional pre-processing step does not adhere consensus and is not detailed in most radiomics studies. Conventionally, the grey-level discretization can be defined as absolute if a fixed bin size is used to cluster intensities of a region of interest within a predefined interval or as relative when a fixed bin number whose size depends on the minimum and maximum intensity values within the same region of interest is preferred. Each method has its own strengths and limitations [95-99], but cannot be used interchangeably. In PET, relative discretization was shown in particular to exhibit higher correlation with the metabolic volume for tumors less than 60 mL[96], whereas it leads to better repeatability in test-retest experiments.[97] In a majority of studies, fixed bin size within a predefined interval has been presented as the default discretization method based on published PET/CT results[95, 100]. This principle is rational for quantitative or semi-quantitative modalities (e. g. HU in CT, SUV in PET) for which intensities have a physical meaning. In MRI, a relative discretization is recommended by the IBSI consortium to account for the variable intensity ranges when no intensity normalization preprocessing step is applied.[29] Note that other discretization approaches exist[98] such as the absolute resampling[96], or the use of a clustering algorithm (Max-Lloyd)[101], but they are currently not included in the IBSI guidelines.

Feature extraction software

There are many free software packages (stand-alone programs, modules and libraries) allowing radiomics feature extraction such as CERR [102], S-IBEX [103], LIFEx [104], MITK [105], RaCaT [106], and PyRadiomics [107]. Even if several studies are still carried out with radiomics in-house developed programs [108-112], use of standardized tools, which must be IBSI-compliant, should be preferred to ensure reproducibility of published data using independent imaging sets.

Feature extraction

Radiomics was originally defined as the extraction of high-throughput features from medical images[11] with the endgoal to identify a limited subset of clinically valuable imaging biomarkers. Radiomics features encompass two broad categories of features: handcrafted features and deep learning features.

Handcrafted features are calculated using predefined mathematical formulas, proposed by experts in human image processing. Handcrafted features include semantic and agnostic features.[10] Semantic features refer to features used in the radiologists' lexicon to describe lesions, but can be evaluated with computer assistance. Agnostic features can be divided into subgroups: (i) shape-based features describing the 3D geometry of the segmented structure, (ii) first-order features quantifying the distribution of voxel intensities, (iii) second-order features, also known as textural features, measuring the statistical relationships between voxels and (iv) higher-order features extracted from filtered-images to analyze repetitive and non-repetitive patterns. All of these handcrafted features are also known as traditional radiomics features.

Deep-learning features are automatically extracted from medical images by neural networks designed to answer to a classification or a regression problem. They are increasingly used in radiomics as they reduce the need for medical expertise for lesion contouring, and remove the inter-expert variability. In addition, they do not necessitate any prior knowledge about predefined features to be extracted. Recent works demonstrated the superiority of deep-learning features compared to handcrafted features in large datasets.[113-115]

Machine-learning strategies and overfitting

Ideally, radiomics studies should provide clinically meaningful decision tools, after having been trained/validated on large multicentric datasets, and thoroughly tested on a previously unseen large multicentric dataset, ideally prospectively collected after the training/validation step. Nonetheless, a recent review of imaging studies demonstrated that only 6% of radiomics studies fulfill these rigorous but mandatory requirements.[26]

The problem is that AI is so powerful at handling complex multidimensional data that it can easily draw false correlations. Overfitting defines the fact that high dimensional models and associated AI training algorithms 'memorize' that a specific combination of parameters is linked to the data being used for training. In other terms, AI learns a model that addresses perfectly the prediction task on the training set but will fail to predict future observations from new sets of data. One key limitation is, therefore, that training robust AI approaches requires techniques that generalize well. This can be achieved either by using a large representative sample set of training or integration of domain knowledge and clinically inspired imaging biomarkers.

Recent papers have detailed good practices guidelines for radiomics model building and evaluation.[13, 53, 116]

Applications of machine-learning analysis of radiomics features in radiation therapy: state-of-the art

Overview

Overall, we identified a few articles reporting negative results [118-121] while we identified 161 manuscripts deciphering positive results on the potential impact of radiomics on patients' care based on CT-scan, MRI, and PET (**Table 1**) using as keywords "Radiotherapy AND (CT OR MRI OR PET) AND (Radiomics OR texture)" on Pubmed.

In Figure 1, we provide a summary of our results by primary tumor site (**Fig. 1A**), classification task (**Fig. 1B**), sample size (**Fig. 1C**), publication year (**Fig. 1D**), type of data collection (**Fig. 1E-F**) and type of model performance evaluation (**Fig. 1G**).

Radiomics and machine learning were mainly used for prognosis (n=75, 45%) and response prediction (n=44, 27%). Other tasks, such as classification (n=23, 14%), segmentation (n=10, 6%), or prediction of toxicity (n=11, 7%) were less frequent (**Fig. 1B**). **Figure 2** shows an overview of these applications based on the current literature. The most important use of radiomics was for prognostic purposes: the stated aim was to derive a progression-free survival or overall survival tool. The second was the use of radiomics for predictive purposes: the radiomics variables were selected for their ability to predict tumor sensitivity to treatment, based on a gold standard evaluator, whether radiological (e.g. RECIST criteria) or histological (complete vs. incomplete pathological response). The third most common use of radiomics was for classification tasks that did not fall into one of the above categories. The vast majority of papers focused on binary classification tasks which are suitable for most machine-learning algorithms but might not encompass the complexity of clinical classification tasks.

Most of studies were retrospective (n=152, 93%) while only a dismal amount of studies have used prospective datasets (n=12, 7%) (**Fig. 1E**). Similarly, most studies were performed in a monocentric setting (n=149, 91%) while a minority was performed in multiple institutions (n=15, 9%) (**Fig. 1F**). Finally, half of studies presented results only in the training dataset (n=73, 44%) (**Fig. 1G**). Stringent validation strategies such as validation and test sets (n=4, 2%) should be the norm. Nonetheless, a vast majority of studies did not use such rigorous approach and relied on cross-validation (n=35, 21%), use of a validation set (n=40, 24%), or cross validation and test sets (n=12, 7%). Cross-validation refers to a principle of creating several partitions of the data set between training and testing and reporting the aggregated results. Validation set can be envisioned as an extension of the training set, which should be used to fix hyper-parameters and/or evaluate if the model developed in the training set generalizes well. The test set is an external data set that should have the same probability distributions than the training partition and on which the results are reported once the algorithm has been trained and already evaluated on a validation set. It should be used once only.

The heterogeneity of the literature is further accentuated by the variety of imaging techniques explored. In CT scan, the current literature is mostly derived from the analysis of standard of care images. Nonetheless, contrast-enhancement protocols are variable. Most PET-CT studies used 18F-FDG as a radiotracer (59/63 = 94%). In MR, in addition to anatomical T1 and T2 sequences, about 40% of studies analyzed functional Diffusion-Weighted Imaging (DWI).

Sample size

The median [interquartile range] number of patients was 64 [29.5-125.5]. A majority of studies included more than 50 patients (n=101, 61%) (**Fig. 1C**). Nonetheless, a minority of studies

reached sample sizes that would allow high dimensional models and machine learning approaches to be statistically robust such as >100 patients (n=57, 35%) or >200 patients (n=24, 15%). Hence, the robustness of the results as well as the actual predictive performance are likely overestimated by most studies due to probable overfitting: the performance of existing algorithms was indeed not applied to large new datasets in most studies. This is further accentuated from the lack of multi-centric data cohorts as pointed earlier.

Primary tumor type

The primary tumor localization in these articles was: head and neck (n=40, 24%), anorectal (n=28, 17%), lung (n=29, 17%), brain (n=24, 15%), prostate (n=14, 9%), esophagus (n=13, 8%), cervix (n=11, 7%), bone (n=4, 2%), breast (n=2, 1%), pancreas (n=2, 1%), neuroendocrine tumors (n=1, 1%) (**Fig. 1A**). A few articles used mixed cohorts (lung-cervical and lung-head and neck), respectively to assess the risk of remote relapse and to evaluate the ability of radiomics to distinguish between healthy and pathological tissue.[117, 122, 123]

Milestones

We could not clearly identify a subset of radiomics biomarkers with major clinical value across several studies since there was a wide range of distinct clinical endpoints and statistical approaches. Additionally, these results cannot yet be translated from bench to bedside to personalize patients' management. First, the vast majority of studies do not demonstrate the added value of radiomics as compared to existing reference standards or widely available clinical decision tools (i.e., tumor volume, stage, RECIST). Additionally, there is a clear need to standardize feature calculation and machine-learning pipelines so that results can be compared from one institution to another. Finally, there is a need to prospectively validate these results.

Reporting negative results

The existing results should be considered with caution since the few negative results published in the literature might just be the tip of the iceberg.[118-121] This can be explained by several factors previously described such as the relatively small size of existing datasets, the heterogeneity in image acquisition or the absence of signal in the images.

A retrospective study reported negative results in 726 CT and 686 PET images from head and neck cancer patients, who were divided into training or validation cohorts. A quantification of tumor volume alone was found to be the best imaging biomarker for the prediction of overall survival while adding radiomics features provided no incremental value.[118]

Another retrospective study trained a radiomics signature in 141 NSCLC patients treated with curative intended (chemo)radiotherapy. To this end, they extracted features quantifying change in tumor imaging phenotype extracted from cone-beam CT (CBCT) images. The authors aimed to validate the results in three external validation datasets of 94, 61 and 41 patients. Strikingly, the

authors could not confirm their hypothesis that longitudinal CBCT-extracted radiomics features contribute to improved prognostic information for the prediction of patients' outcome.[119]

Similarly, a PET radiomics study with a moderate sample size was not able to identify prognostic features for overall survival in a cohort of patients with NSCLC. [120]

Radiomics machine-learning using CT images

The majority of articles evaluated the use of radiomics-based machine learning algorithms as a prognostic tool. The largest study investigated the prognostic value of CT images in head and neck cancer. It was a pivotal publication in the field of radiomics and presented a radiomics analysis of 440 features quantifying tumor image intensity, shape and texture in 1,019 patients with lung or head-and-neck cancer. It demonstrated that intratumor heterogeneity on CT scan images was associated with underlying gene-expression patterns and suggested a general prognostic phenotype existing in both cancer types.[117] Nonetheless, recent studies reanalyzing this seminal work and pioneer radiomics signature showed that the performance of the signature was due to tumor volume alone and that other radiomics features were not providing additional value.[121]

There is a growing number of studies evaluating the value of radiomics analysis of CT-scans in large cohorts.[108, 122, 124-130] Pioneering papers demonstrated the concept that radiomics features extracted from CT-scans could have clinical value in cancer patients with lung cancers[122, 128, 129], and head and neck cancers[122, 125] treated with radiation therapy. A wide range of models have been developed predicting endpoints associated with patients' outcome such as stage [122], HPV status [122], pathologic gross residual disease [129], distant metastasis[128], and pathologically proven local treatment failure.[125] These studies demonstrated the value of a subset of imaging biomarkers deciphering tumor imaging phenotype before treatment initiation. The most frequently identified biomarkers were respectively tumor intensity [125, 128, 129], tumor texture [125, 128, 129], tumor shape [128, 129], and multiscale filters [129]. Additionally, temporal changes using dual time points or multiple time points in these features could further enhance clinical decision-making and forecast treatment efficacy.[131-133] These imaging biomarkers deciphering temporal changes in tumor volume, tumor shape, and tumor spatial heterogeneity seem to be features generalizable beyond image-guided radiation therapy since they can be leveraged to predict systemic therapies efficacy.[134, 135] This creates a body of evidence pointing in the same direction.

Interestingly, methodological considerations for the optimization of radiomics machine-learning pipeline using CT features have been extensively investigated in patients with lung and head and neck cancers.[123, 124, 126] Reliable machine-learning methods[123] and robust radiomics strategies[126] were identified for radiomics-based prognosis. Additionally, it has been demonstrated that although the presence of CT artifacts could be problematic, it does not preclude designing robust radiomics signatures for prognosis.[124]

CT features have also been used with the aim to predict radiation-induced toxicity. For instance, a population of 106 patients who received radiation therapy for esophageal cancer was studied.[130] It was shown that the change between pre and post-RT CT-scans in 12 radiomics texture-based features was associated with radiation pneumonitis. In another study, the objective was to perform toxicity prediction primarily for patients with head and neck cancer.[136]

As a conclusion, several studies evaluated the performance of models derived from machine-learning analysis of radiomics features on CT-scan. The reported results certainly bear promise but the added value of AI-based clinical care needs to be prospectively validated in randomized multicenter trials with a comparison to the optimal standard of care. This is a necessity towards further clinical adoption.

Radiomics machine-learning using PET images

The majority of articles evaluated radiomics as a prognostic tool. The largest study investigated the prognosis value of PET derived shape, intensity, and textural features for the prediction of overall survival in patients with lung cancer.[137] It included 358 patients from 7 different centers, divided into training, validation, and an external testing cohort (133:204:21). Least absolute shrinkage and selection operator (LASSO)[138] was used to identify 2 features (size-variance of the grey-level size zone matrix, complexity of the neighborhood grey tone difference matrix) that can stratify high versus low risk patients when linearly combined. It is noteworthy to mention that the radiomics features were robust with respect to the adopted semi-automatic segmentation. The signature was also robust with respect to PET clinical acquisitions across manufacturers/vendors. Finally, only the total metabolic volume (TMTV) and the total lesion glycolysis (TLG) were proven as prognostic features among routinely extracted SUV-based parameters, but their performance was less significant compared to features that were automatically recovered from the model. The main limitation of this analysis, also pointed out by the authors, was the lack of comparison with the common clinical prognostic factors (such as performance status for example), and the unusual survival distribution in the test set, making it insufficient for complete external validation. The discrepancy of population statistics between testing and validation cohorts is a major bottleneck as it concerns generalization claims of the radiomics-driven machine learning prediction methods.

The second largest PET study [139] had as an objective to evaluate radiomics features on the tumor nodes and not only on the primary tumor. The study population was divided into training and validation sets (262:50). Again, an initial verification of the robustness of the radiomics features was performed, before introducing them into a multivariate LASSO model. The consistency of the features was analyzed by comparing features extracted from the whole diseased lymphatic volume, to features retrieved from the most hypermetabolic lymph node and from the largest lymph node. A multivariable model including one feature from the primary tumor and five features from the lymph nodes was evaluated and achieved a c-index of 0.62. Regarding this study, two observations should be

emphasized: first, the lack of prognostic character of the usual metabolic parameters of the primary tumor is in agreement with the results of the previous study. Second, the only texture parameter of the primary tumor that was prognostic for overall survival was not part of the ones found in the previously described study (GLRLM short-run emphasis).[137]

Within tens of studies regarding esophageal cancer, we have noticed that there was a single study involving more than 100 patients.[140] This paper had the particularity of using pre- and post-therapy PET-CT to evaluate the ability of texture parameters to predict the complete pathological response on histology. The design of this study made it possible to evaluate the incremental contribution of extracted texture parameters compared to conventional parameters and visual analysis by the medical expert. A clinical impact study was also conducted. Unfortunately, it was observed that the impact of the new texture parameters on patient management was rather limited: the increase in the ability to discriminate between complete and incomplete histological response was insufficient to translate into clinical recommendations.

Very few studies have focused on the ability of PET textural parameters to predict radiation toxicity. Among them, the most interesting [141] studied the salivary toxicity in patients irradiated for head and neck cancer. The reported results were not convincing enough to justify the adoption of the study outcomes into clinical practice. Indeed, there was a very moderate increase in the discriminating capacity of the model compared to the reference model based on gland dose. Moreover, from a methodological point of view, the results appear to lack robustness and generalization and were not independently validated.

Radiomics machine-learning using MR images

The majority of studies used radiomics for prognosis (n=23/86, 27%) and response prediction (n=32/86, 37%). Interestingly, radiomics or texture analysis was also used for segmentation tasks, toxicity prediction and other classification tasks such as differentiation of true progression from pseudo-progression in brain lesions or pre-treatment identification of eligible patients for adaptive radiotherapy in head and neck cancer.

In terms of prognosis, existing literature evaluated a great diversity of primary tumor types, with applications in cervical cancer[110], osteosarcoma[142], brain tumors[143, 144], head and neck[145] and skull-base chordoma.[146] Three papers aimed at developing a nomogram based on multidimensional data.[144-146] A nomogram including radiomics features extracted from the regional lymph nodes, treatment plan metrics, and TNM stage was shown to outperform score of TNM alone for prediction of the 3 and 5-years progression free survivals in histologically confirmed loco-regionally advanced nasopharyngeal carcinoma (stage III-IVa).[145] Using a cohort composed of 148 skull base chordoma patients, a nomogram including histological subtype, blood supply and a radiomics signature was developed in [146], showing promising results for prediction of progression risk at 5 years compared to a clinical prognosis model.

Six studies with a data cohort beyond 100 patients investigated the performance of models predicting pathological complete response to neoadjuvant radiotherapy in locally advanced rectal cancer with a validation strategy. Two carried out a delta-radiomics analysis based on pre and post radiotherapy MR images[131, 147], whereas the others analyzed either pre-treatment images only[148, 149], or pre and post-treatment MR images in an independent manner.[150, 151] The obtained ROC-AUC for two of them was superior to 0.95 in their validation cohorts. The first study has explored a signature of 30 pre and post-treatment radiomics features plus the post-treatment tumor length[151] while the second one was developed on the basis of 12 pre-treatment radiomics features plus the MR-reported T-stage. Sensitivity and specificity values were however lacking despite the notable class imbalance in the dataset.[151] Both papers highlighted the informative content of ADC maps for prediction of complete pathological response in locally advanced rectal cancer.

The prediction of radiation-induced toxicities based on pre-treatment MR images has also gained attention even radiomics driven AI models failed to reach strong performances. Radiomics features were extracted from salivary glands of baseline CT plus T1 post-contrast MR images from 216 patients and a generalized linear regression model was developed to predict radiation-induced xerostomia at 3-months after radiotherapy.[152] In the independent testing cohort including 50 patients, ROC-AUC values inferior to 0.7 were obtained, suggesting limited signal in baseline images. In this paper, a rigorous evaluation methodology was adopted including cross-validation plus testing cohort.

Classification performances of radiomics for distinguishing true progression vs. radionecrosis in brain metastasis after stereotactic radiotherapy were evaluated in two papers.[22, 23] The paper including the highest number of patients enrolled 87 patients and explored 97 lesions treated by Gamma Knife radiosurgery[23] at two time points (interestingly, delta radiomics was normalized according to the delay between the two time points). MR images acquired at two time points were also used to select features having a high Concordance Correlation Coefficient (CCC > 0.7) in the tumor progression group and low CCC comparing tumor progression and radionecrosis groups. The best results were obtained using 5 delta radiomics features: a ROC-AUC of 0.73 was achieved using a leave-one-out cross-validation. Slightly better classification results were obtained using features extracted from post-contrast T1 and FLAIR sequences acquired at a unique time point.[22] No common radiomics feature was identified between the two signatures.

In a different clinical setting, the study of advanced nasopharyngeal carcinoma patients who will require a radiotherapy treatment adaptation was done on pretreatment MRI.[153] Average ROC-AUC in validation set was 0.930 (95%CI: 0.928–0.933) and included 6 radiomics features for the joint T1-T2 model. One drawback is that only 13 patients out of the 70 patients included in the study required a treatment adaptation.

Even if the majority of radiomics papers considered tumor volume as a whole, some papers applied classification tasks at a voxel scale with the goal to improve tumor delineation and associated

treatment planning. The estimation of the peritumoral infiltration and the associated recurrence risk using radiomics features for de novo glioblastoma patients was studied in [72]. In this work, pre-operative MR images were considered and assumptions were made on the quantity of infiltration in edema regions to train a support-vector machine classifier based on a discovery cohort including 31 patients and a leave-one-out cross-validation strategy. Performances were then evaluated on a validation cohort with similar population characteristics (n=59 patients), by reporting manually recurrence areas on pre-operative images. Encouraging results were obtained with prediction accuracy equal to 89.5% (sensitivity: 97.1%, specificity: 76.7%). Authors concluded on the possibility to guide supratotal resection and/or intensification of postoperative radiotherapy based on multiparametric clinical MR sequences. A radiomics-based radiotherapy planning strategy was proposed with the ultimate goal to focalize RT for low risk patients and to escalate the dose to the most aggressive areas for intermediate/high risk patients.[154] In this multi-institutional work, more than 300 features were extracted from T2w and DWI MR sequences to identify probability of cancer presence. On the replication cohort, ROC-AUC between 0.5 and 0.8 were obtained using T2w sequence-radiomics features only on a patient basis. Subsequent dosimetric results suggested that radiomics-targeted focal brachytherapy would result in a marked reduction of doses to OAR and that the choice of a boost-radiomics-based strategy to the aggressive tumor components would lead to a limited increase of doses to OAR.

Discussion and perspectives

AI and more specifically machine learning analysis of radiomics features is currently a promising tool in clinical research to optimize the management of cancer patients treated with radiation therapy. With the advent of AI, medical images move from clinically relevant radiological information that are subjectively interpreted by clinicians to high dimensional multiparametric data that is exploited by algorithms to reproducibly optimize clinical care in radiation therapy based on evidence. **Figure 3** illustrates how these technologies could potentially enhance patient care in future AI-based radiotherapy workflow. We have observed that radiomics is used for several clinical tasks such as prognosis, treatment implementation, response assessment, prediction of recurrence/relapse, and prediction of toxicity. The dominant indication is prognostication for risk stratification. The following paragraphs will summarize the current state-of-the art, describe our vision of what radiomics can bring for precision care, and outline next steps required to translate radiomics research from bench to bedside.

While several guidelines/opinions/reviews deciphered the role of machine learning and radiomics as a potential tool for precision medicine [13, 26-30], the present work aimed to explore the existing literature in the field of radiation therapy. It exposes current technical caveats that should be overcome in the future for the deployment of radiomics in a clinical radiotherapy workflow. Our

objective was to precisely describe, using a step-by-step approach its current evaluation for a range of clinical problems addressing prognostication, treatment planning, response assessment, prediction of recurrence/relapse, and prediction of toxicity. Finally, an innovative part of our work was to evaluate multiple modalities since we aggregated data from 165 original research studies reported results on PET, CT-scan, and MRI.

The first step of the radiomics pipeline is to choose the optimal imaging modality or the best combination. We have demonstrated that the majority of studies are focusing on imaging modalities used in clinical routine such as CT-scan, anatomical and functional MRI, and 18F-FDG PET/CT. This can be explained by the fact that machine-learning requests big data, hence the current use of retrospective datasets to prove the concept that these features could be of clinical utility. However, we have to keep in mind that radiomics biomarkers are in fact surrogate markers of complex metabolic pathways (**Fig. 4**). Beyond these mainstream imaging modalities, several radiotracers could be explored to improve patients' management in the field of radiation therapy alone or in combination with systemic therapies (such as chemotherapies, targeted agents and immunotherapies) and are key to understand correlations between conventional CT or MR imaging patterns and biological pathways. The next breakthrough in machine-learning analysis of radiomics features could be to use the information provided by this untapped resource of molecularly targeted compounds. These tracers can indeed be used to quantify a wide range of critical pathways including amino acid metabolism (^{18}F-FET: fluor-18 Fluoro-ethyl-L-tyrosine, AMT: alpha-^{11}C-L-methyltryptophan, ^{18}F-FDOPA), DNA synthesis (^{18}F-FLT: 3'-(^{18}F)-Fluoro-3'-deoxythymidine), membrane proliferation (^{18}F-fluorocholine), angiogenesis and perfusion (H2^{15}O PET, ^{18}F-AlF-NOTA-PRGD2 PET, ^{18}F FPPRGD2 PET), hypoxia (^{15}Oxygen, ^{18}F-FMISO: ^{18}F-Fluoromisonidazole, ^{18}F-FAZA: ^{18}F-1-(5-fluoro-5-deoxy-α-D-arabinofuranosyl)-2-nitroimidazole), and mitochondrial activity (TSPO: the mitochondrial translocator protein, ^{18}F-GE-180).[155] Regarding immune contexture, surrogate CT-based radiomics signatures have been proposed in the literature and shown to correlate significantly with tumor-infiltrating CD8 cells and responses of patients to immunotherapies.[14] Beyond CT-scan, new radiotracers have been developed to decipher immune contexture *in vivo* such as PD-1/PD-L1 imaging[156], CD8 imaging[157], tumor-associated macrophages imaging[158], and interleukin-2 imaging.[159] Therefore, the way forward could be to combine CT-scan or MR to molecularly targeted imaging with the ultimate goal to increase prediction performance and guide clinical care with great accuracy.

The second step is to define the volume of interest, which will be used to extract imaging features on which machine learning methods will seek to determine prediction. The delineation process is critical since it determines the imaging input for RT planning (**Fig. 3**) and may also ultimately alter the performance and the generalizability of radiomics models. The accuracy of high precision image guided delivery techniques is hampered by potential deviations in target and OAR volume delineation (**Fig. 3**). Hence, the current development of AI-based automatic segmentation tools to allow for an objective and reproducible segmentation.[160-162] These solutions are based in a

majority of cases on deep-learning networks, which have been shown to outperform multi-atlas algorithms.[163, 164] Nonetheless, the dosimetric and clinical impacts of automatic contours still need to be compared to the current "gold standard" manual contours.[165] As well, automation of treatment planning will be required to reduce dependence on planners' expertise. Both steps, in addition to standardize RT treatments, will be of importance to increase quality of clinical data, which are vital inputs for evidence-based medicine.

The third step of an AI-based pipeline would be an AI-assisted treatment planning, treatment adaptation, and post-treatment management including optimization of patients' follow-up, individualized risk stratification, and personalized adjuvant therapy **(Fig. 3)**. A vast majority of articles have evaluated radiomics as a prognostic tool that could be used for risk stratification using CT, MR, and 18F-FDG PET scans. These results suggest that a subset of imaging biomarkers that decipher tumor phenotype before treatment initiation could be used to detect patients with poor prognosis. These imaging biomarkers can be understood as surrogates for tumor vascularity, glucose metabolism, surrounding tissue infiltrativeness, and heterogeneity, which are biologically intuitive but need to be validated prospectively.

Development of MR-based multi-parametric imaging treatment planning solutions will be accentuated from the clinical adoption of MR-Linacs. Such innovative planning and treatment implementation solutions could drastically change the radiotherapy landscape and might be leveraged by radiomics studies. MR-based dosimetry and MR-based treatment implementation open the way to daily/weekly non-ionizing anatomical and functional imaging, which will surely contribute to precision medicine.[166] Better contrast in soft tissue regions will improve accuracy in patient positioning and probably decrease planning target volumes margins for several cancers such as pelvic, and head and neck tumors.[166, 167] Additionally, possibilities in treatment adaptation based on geometrical changes, already permitted thanks to on-the-fly treatment planning tools, will probably help improve local control and decrease toxicities.[167] In adaptive MR-based radiotherapy, we can hypothesize that next steps will be incorporation of radiomics for modification of prescription at a certain time point depending on tumor response. However, intensive use of imaging on table will probably require short-time acquisitions possibly leading to images of inferior quality compared to diagnostic images.[168] Radiomics could still help in this particular field by potentializing low-quality imaging by retrieving biological content from noisy signals. Role of deep-learning will be interesting also in this field for image quality improvement and signal denoising.[169]

Modifications in dosimetry strategies have also to be evaluated by clinical trials to validate hypothesis that focalized RT does not decrease local control for low risk patients and that dose escalation to most aggressive areas, which has been shown to slightly increase OAR doses in a theoretical dosimetry analysis[154] focused on prostate cancer, has a substantial impact for intermediate/high risk patients. Literature is scarce regarding the use of conventional radiomics for the prediction of loco-regional recurrence areas.[72, 170, 171] In prostate cancer, work should be pursued

to understand correlations between multiparametric MR and associated 3D maps of voxel-based radiomics features and tissue categories. In brain tumors, for which a bulk resection of the tumor is often impossible, mapping of MR acquired at the recurrence time on pre-radiotherapy MR appears to be an alternative for developing models quantifying probabilities of relapse.[172] Strategies are here to be defined for dose redistribution and dose painting implementation.[173] A suggestion could be the deduction of TCP curves describing the probability of killing tumor cells as a function of the received dose and recurrence probability, and the implementation of optimizers maximizing patient's tumor control probability for a prescribed dose. On this topic, randomized clinical trials will then have to be launched to compare patient outcome between conventional RT and AI-based RT. Regarding personalization of dose prescription itself, tumor response and toxicity prediction models will have to be translated into clinical trials in which doses will be personalized depending on individual risk when observational retrospective and prospective studies will have gained maturity. In these clinical trials, one avenue could be to adapt dose constraints, i.e. dose volume histograms clinical goals, to the organs at risk and the target volumes in an individualized manner. Tumor Control Probability (TCP)/Normal Tissue Complication Probability (NTCP) concepts[174] would then have to be revisited to be adapted to individual or sub-groups sensitivity. This is in line with the OSRT (Optimal Stopping Radiotherapy Therapy) concept[175] which aims to personalize TCP and NTCP curves through sequential biomarkers evaluation, with the goal to identify for each patient the optimal time at which to adapt or stop the radiotherapy treatment to improve the therapeutic ratio. Personalized TCP/NTCP curves could also be used earlier in the patient management to determine the best treatment option (e.g. proton vs. photon external beam radiotherapies). In particular, individualized response and toxicity models could feed into clinical decision support systems which have been proposed recently but still suffer from considering population-based radiobiological models.[176]

The final step of future AI-based treatment pipelines would be to archive and aggregate patients' data in multiple institutions so that it can be used to further improve AI models. This is necessity in order to address the existing pitfalls of their clinical adoption that are: standardization, random correlations vs. causality and robustness/generalization. Most of the existing literature has explored the potential utility of machine-learning of radiomics features in archived datasets in a single institution. Therefore, our insight and impression is that the current heterogeneous state-of-the-art is only generating hypotheses that should be validated prospectively since the level of evidence remains speculative. The limitation of most existing research is indeed the lack of quality control, standardization, sufficient sample size and the availability of independent dataset for testing. Another important point is the need of comparison of radiomics models to already existing models for not substituting simple predictors by complex combinations.[53] Finally, further prospective studies with external validation are needed to translate these results from bench to bedside. At the time at which we are publishing this paper, 32 clinical trials containing the keywords "radiomics" and "radiotherapy" have been reported. Only two of them (NCT0427347, NCT04278274) claim having already built a

radiomics signature they want to validate prospectively. This approach is interesting and should be encouraged in the future. In spite of regulatory constraints and data protection rules, national and international networks initiatives have been developed recently to support precision medicine and AI-based and computer-aided medical programs.[177] These initiatives are of utmost importance to construct collaborative structured annotated databases which will be essential to build robust radiomics models on large cohorts, and evaluate extensively their generalizability.

As a conclusion, this review provides an overview of new concepts, and hypotheses generating findings in the field of machine-learning analysis of radiomics features in cancer patients treated with radiation therapy. Based upon the analysis of 165 original research studies exploring the potential impact of radiomics on patients' care based on CT-scan, MRI, and PET, we describe evolving research trends to enhance several clinical tasks such as prognostication, treatment planning, response assessment, prediction of recurrence/relapse, and prediction of toxicity. This work should be considered as a resource summarizing recent promising applications of radiomics machine-learning in radiation therapy, which potentially may add strong value to patient care.

Tables and figures

Figure 1. Overview of manuscripts on machine-learning analysis of radiomics features applied to Radiation Therapy. (A) Tumor site, (B) Clinical task, (C) Number of patients included in the study, (D) Number of publications per year, (E) Type of data collection (retrospective or prospective), (F) Data source (single center or multicenter), (G) Strategy of model performance evaluation.

Figure 1 legend. Literature review showed increased interest over time for the radiomics field, the most frequent tumor site and machine learning task being head and neck cancer and prognostication respectively. However, most of the data used for radiomics based analysis were monocentric and retrospective, and performance evaluation scheme was not sufficiently rigorous for the majority of articles.

Figure 2. Current applications of radiomics in RT.

Figure 2 legend. Extraction of biomarkers from multimodal images acquired at different time points of the RT treatment (pre, per or post-RT) could help in target volume delineation, dose painting implementation, treatment adaptation, prognostication, treatment response and toxicities prediction and classification between radiation-induced toxicities and tumor progression after the end of the treatment.

Figure 3. Perspective: AI-guided radiation therapy

Figure 3 legend. In the current RT practices, multi-component data including clinical, biological, anatomopathological and genomic data are subjectively analyzed by physicians who prescribe a homogeneous dose to the target volume following a “one dose fits all” concept, i.e. the same prescribed dose for sub-groups of patients. Treatment plan preparation includes subjective manual segmentation and expert-dependent planning. During the treatment, x-ray-based repositioning is mainly used and no treatment adaptation is performed in a large majority of cases.

In our vision of AI-based radiotherapy, large retrospective data collection will be explored to develop multi-component machine-learning models which will help in predicting response and treatment-induced toxicities for each patient. Based on this individualized-risk stratification, personalized doses will be prescribed and dose-volume histograms constraints will be adjusted. As well, AI-based planning will help harmonizing practices. Adaptive RT will become a standard with the democratization of MR-based patient repositioning. AI-assisted follow-up will allow the personalization of adjuvant therapy. Patient data and outcome will be continuously collected for model improvement.

Figure 4. Radiomics machine learning analysis redefines tumor imaging phenotype as a surrogate of molecular pathways

Figure 4 legend. This figure explains the main signaling pathways and radiotracers that currently exist in nuclear medicine and could be used for radiomics machine learning strategies. We have demonstrated that the majority of studies are focusing on imaging modalities used in clinical routine such as CT-scan, anatomical and functional MRI, and 18F-FDG PET/CT. However, we have to keep in mind that radiomics biomarkers are in fact surrogate markers of complex metabolic pathways. Beyond these mainstream imaging modalities, several radiotracers could be explored to improve patients' management in the field of radiation therapy alone or in combination with systemic therapies (such as chemotherapies, targeted agents and immunotherapies). Additionally, future studies should decipher correlations between conventional CT or MR imaging patterns and biological pathways.

Table 1. Use of radiomics and AI in radiation therapy: state of the art

Table 1 legend. The literature search was performed by three independent readers (one per imaging modality). Keywords were "Radiotherapy AND (CT OR MRI OR PET) AND (Radiomics OR texture)". Pubmed was the only database queried. The literature search was performed up to December 2019 for PET, February 2020 for CT and March 2020 for MRI.

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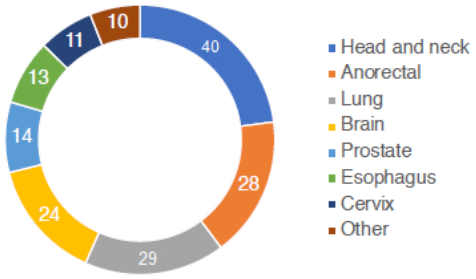
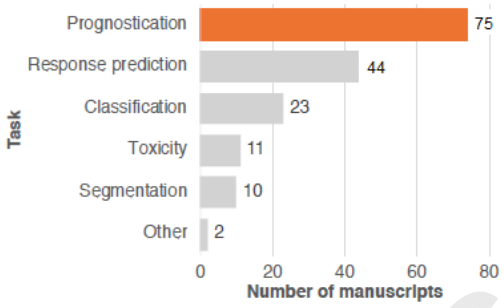
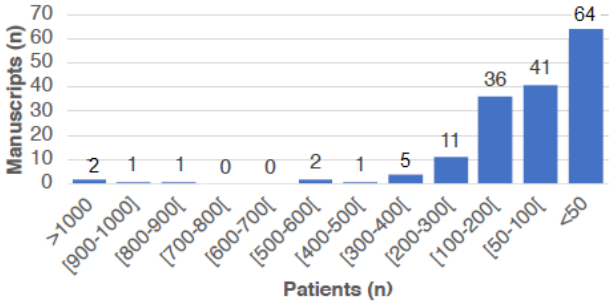
A. Site



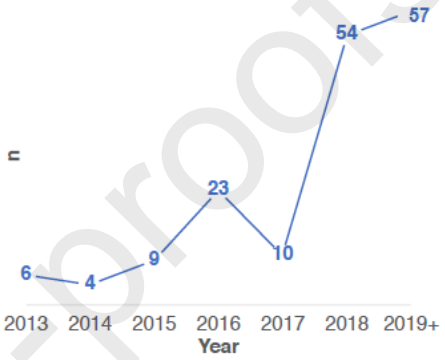
B. Task



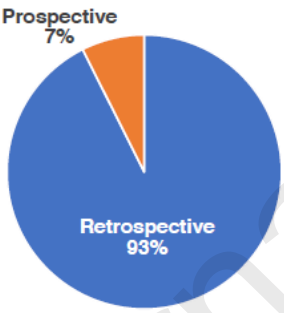
C. Sample size



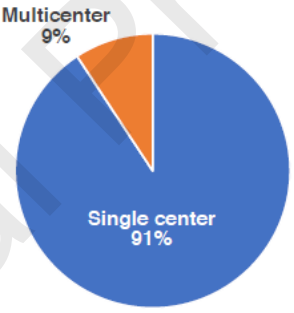
D. Publication per year



E. Data collection



F. Data source



G. Model validation