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Radiation Oncology in the Era of Big Data and Machine Learning for Precision Medicine

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Abstract

Machine learning (ML) applications in medicine represent an emerging field of research with the potential to revolutionize the field of radiation oncology, in particular. With the era of big data, the utilization of machine learning algorithms in radiation oncology research is growing fast with applications including patient diagnosis and staging of cancer, treatment simulation, treatment planning, treatment delivery, quality assurance, and treatment response and outcome predictions. In this chapter, we provide the interested reader with an overview of the ongoing advances and cutting-edge applications of state-of-the-art ML techniques in radiation oncology process from the radiotherapy workflow perspective, starting from patient's diagnosis to follow-up. We present with discussion the areas where ML has presently been used and also areas where ML could be applied to improve the efficiency (i.e., optimizing and automating the clinical processes) and quality (i.e., potentials for decision-making support toward a practical application of precision medicine in radiation therapy) of patient care.

Keywords: big data, machine learning, radiation oncology, decision-making, precision medicine

1. Introduction

Radiation oncology is the discipline dealing with the treatment of malignant neoplasias or cancerous lesions (and occasionally benign lesions) with ionizing radiation for cure or palliation intent. The clinical modality or technique has been used to treat the patient in radiation oncology is referred to as radiation therapy (or “radiotherapy”). Radiotherapy has often given in combination with other treatment modalities for instance chemotherapy, surgery, hormonal therapy, etc. The aim of radiotherapy is to deliver a precisely measured dose of irradiation to a defined tumor volume with as minimal damage as possible to surrounding healthy tissue, resulting in eradication the tumor, high quality of life, and prolongation of survival [1]. **Figure 1** presents a typical radiotherapy workflow, from patient consult and assessment to follow-up. The field of radiotherapy has witnessed with significant technological advances over the last decades. This advancing has introduced the complexity of radiotherapy processes and generating a massive amount of data (also so-called “big data”) during radiotherapy workflow.

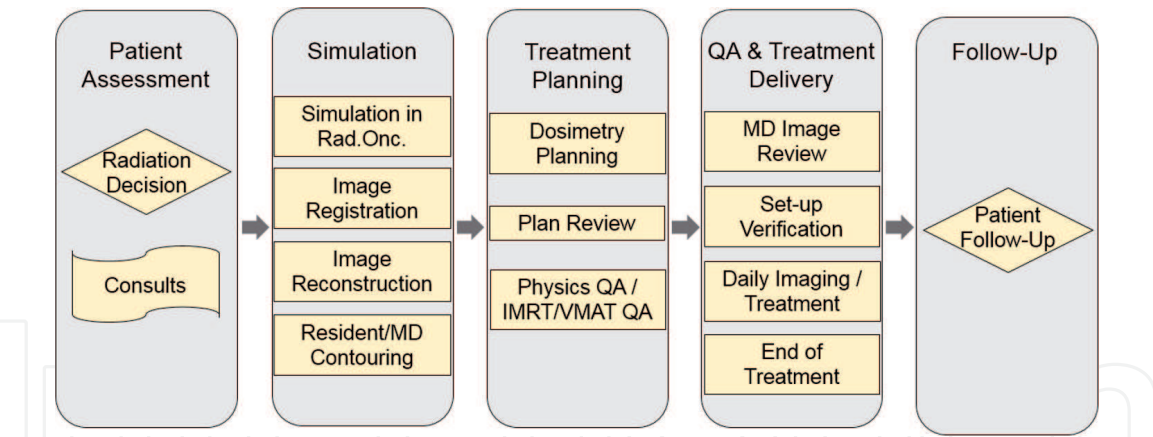


Figure 1.
Radiotherapy workflow, from patient consult and assessment to follow-up.

1.1 Big data

Big data is data which is of a large volume, often combining multiple data sets and requiring innovative forms of information technology to process this data [3]. Big data has characterized by four V's: volume, variety, velocity and veracity [3]. In radiation oncology, data can be categorized as “Big Data” because (a) the use of data-intensive imaging modalities (volume), (b) the imaging archives are growing rapidly (velocity), (c) there is an increasing amount of imaging and diagnostic modalities available (variety), and (d) interpretation and quality differs between care providers (veracity) [4]. The radiation oncologists are overwhelmed with scientific literature, rapidly evolving treatment techniques, and the exponentially increasing amount of clinical data [5]. **Figure 2** shows more and more information is associated with the patient as the proceeds along the radiotherapy process, like a snowball rolling down a hill [2]. The radiation oncologists need help translating all these data into knowledge that supports decision-making in routine clinical practice [6–10].

In this direction, such collaborative efforts have been established in the last few years to advance the possibilities of using big data to facilitate personalized clinical patient care in the field of radiation oncology. For example, in 2015, the American Society for Therapeutic Radiation Oncology (ASTRO), National Cancer Institute (NCI), and American Association of Physicists in Medicine (AAPM) co-organized a workshop with aims focused on opportunities for radiation oncology in the era of big data [9]. Later in 2017, the American College of Radiology (ACR) has established the Data Science Institute (DSI) with a core purpose to empower the advancement, validation, and implementation of artificial intelligence (AI) in medical imaging and the radiological science for the benefit of patients, society, and the profession [10].

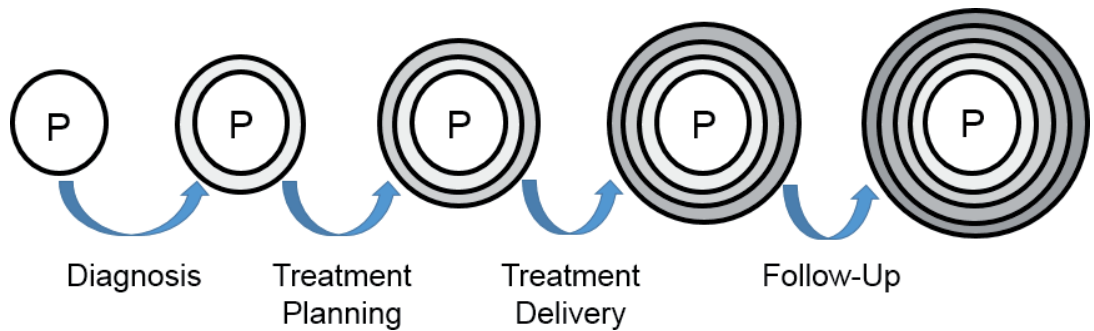


Figure 2.
With each step along the radiotherapy workflow, more information is created and collected which has associated with the patient (reproduced from [2]).

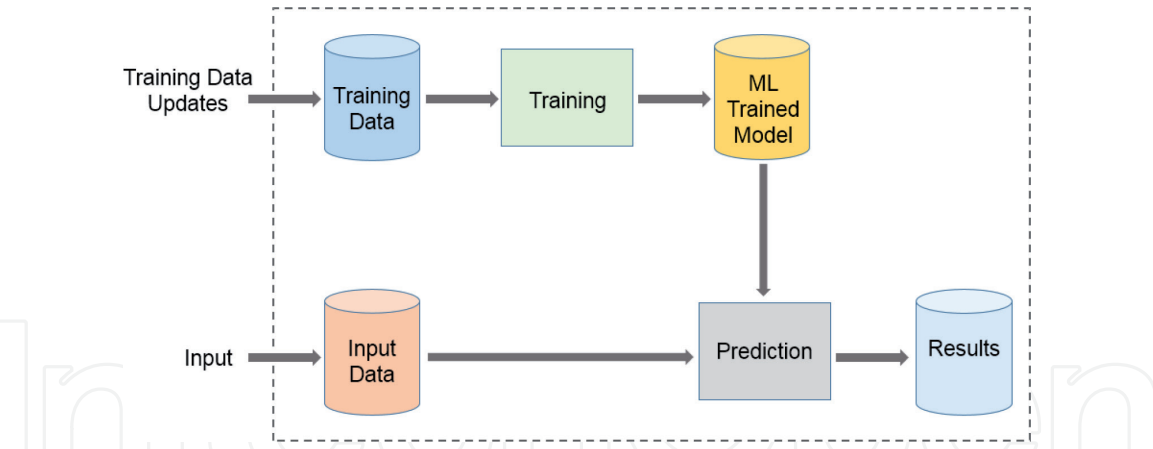


Figure 3.
A generic machine learning workflow.

1.2 Machine learning

Machine learning (ML), a branch of artificial intelligence, is the technology of developing computer algorithms that are able to emulate human intelligence. An ML algorithm is a computational process that uses input data to achieve the desired task without being literally programmed (i.e., “hard-coded”) to produce a particular outcome [2]. These algorithms are in a sense “soft-coded” in that they automatically alter or adapt their architecture through repetition (i.e., experience) so that they become better and better at achieving the desired task [2]. The process of adaptation is called training, in which samples of input data have provided along with desired outcomes [2]. The algorithm then optimally configures itself so that it cannot only provide the desired result when presented with the training inputs, but it can even generalize to produce the desired outcome from new data [2]. **Figure 3** shows a generic ML workflow. In which, the ML model is trained first on a training data then the trained model is used for predicting the results for new data [2]. More deeply, ML algorithms have been classified according to the nature of the data labeling into supervised (e.g., classification or regression), unsupervised (e.g., clustering and estimation of probability density function), and semi-supervised learning approach (e.g., text/image retrieval systems) [11–13].

With the era of big data, the utilization of machine learning algorithms in radiation oncology research is rapidly growing. Its applications include treatment response modeling, treatment planning, organ segmentation, image-guidance, motion tracking, quality assurance, and more. In this chapter, we provide the interested reader with an overview about the ongoing advances and cutting-edge applications of the ML methods in radiation oncology from a workflow perspective, from patient diagnosis and assessment to treatment delivery and follow-up. We present the areas where ML could be applied to improve the efficiency, i.e., optimizing and automating the clinical processes, and quality, i.e., potentials for decision-making support toward precision medicine in radiation therapy, of patient care. This chapter is organized as follows: Section 1 provides introduction to radiation oncology, big data, and machine learning concept; Section 2 illustrates an overview of the utilization of machine learning methods in radiation oncology research from a workflow perspective; Section 3 discusses limitations and the challenges of the of the current approaches as well as the future vision to overcome these problems; and Section 4 presents conclusions.

2. Machine learning in radiation oncology

The utilization of machine learning algorithms in radiation oncology research has covered almost every part in radiotherapy workflow process (**Figure 1**). ML

techniques could compensate for human limitations in handling a large amount of flowing information in an efficient manner, in which simple errors can make the difference between life and death. Also, it would allow improvements in quality of patient care through the potentials toward a practical application of precision medicine in radiation oncology. In this section, we go over each part in the radiation oncology workflow (**Figure 1**) process presenting studies that have been conducted with machine learning models. The radiation oncology workflow starts with patient diagnosis and assessment, to treatment simulation, to treatment planning, to quality assurance and treatment delivery, to treatment outcome and follow-up.

2.1 Patient diagnosis, assessment, and consultation

The radiation oncology process begins at the first consultation. During which, the radiation oncologist and patient meet to discuss the clinical situation to determine a treatment strategy [14]. The stage that precedes the patient assessment and consultation is a patient diagnosis, in which patient with cancer disease identified on medical images and then pathologically confirmed the disease. Machine learning toolkits such as computer-aided detection/diagnosis have been introduced for identifying and classifying cancer subtypes (staging). For example, lesion candidates into abnormal or normal (identify and mark suspicious areas in an image), lesions or non-lesions (help radiologists decide if a patient should have a biopsy or not), malignant or benign (report the likelihood that a lesion is malignant), etc. Machine learning plays a crucial role in computer-aided detection/diagnosis toolkits, and it could provide a “second opinion” in decision-making to the physician in diagnostic radiology.

2.1.1 Computer-aided detection

Computer-aided detection (CADe) has defined as detection made by a physician/radiologist who takes into account the computer output as a “second opinion” [2]. CADe has been an active research area in medical imaging [2]. Its task is classification based solving a problem, in which the ML classifier task here is to determine “optimal” boundaries for separating classes in the multidimensional feature space. It focuses on a detection task, e.g., localization of lesions in medical images with the possibility of providing the likelihood of detection.

Several investigators [15–18] have developed ML-based models for detection of cancer, e.g., lung nodules [15] in thoracic computed tomography (CT) using massive training artificial neural network (ANN), micro-calcification breast masses [16] in mammography using a convolutional neural network (CNN), prostate cancer [17] and brain lesion [18] on magnetic resonance imaging (MRI) data using deep learning. Chan et al. [16] achieved a very good accuracy, an area under a receiver operating characteristic curve (AUC) of 0.90, in the automatic detection of clustered of breast microcalcifications on mammograms. Suzuki et al. [15] reported an improved accuracy in the detection of lung nodules in low-dose CT images. Zhu et al. [17] reported an averaged detection rate of 89.90% of prostate cancer on MR images, with clear indication that the high-level features learned from the deep learning method can achieve better performance than the handcrafted features in detecting prostate cancer regions. Rezaei et al. [18] results demonstrated the superior ability of the deep learning approach in brain lesions detection.

Overall, the use of computer-aided detection systems as a “second opinion” tool in identifying the lesion regions in the images would significantly contribute to improving diagnostic performance. For example, it would lead to avoid missing cancer regions, increase sensitivity and specificity of detection (increased accuracy), and diminish inter- and intraobserver variability.

2.1.2 Computer-aided diagnosis

Computer-aided diagnosis (CADx) is a computerized procedure to provide a “second objective opinion” for the assistance of medical image interpretation and diagnosis [19]. Similar to CAdE, its task is a classification solving-problem. CADx focuses on a diagnosis (characterization) task, e.g., distinction and automatically classifying a tumor or lesion being malignant or benign with a possibility of providing the likelihood of diagnosis.

Numerous studies [19–22] have demonstrated the application of CADx tools for diagnosing lung [19–21] and breast [19, 22] lesions. Cheng et al. [19] investigated the deep learning capability for the diagnosis of breast lesions in ultrasound (US) images and pulmonary nodules in CT scans. Their results showed that the deep-learning-based CADx can achieve better differentiation performance than the comparison methods across different modalities and diseases. **Figure 4** illustrates several cases of breast lesions and pulmonary nodules in US and CT images, respectively, differentiated with deep learning-based CADx [19]. Feng et al. [20] and Beig et al. [21] studied the classification of lung lesions on endo-bronchoscopic images [20] with logistic regressions, and non-small cell lung cancer (NSCLC) adenocarcinomas distinctions from granulomas on non-contrast CT [21] using support vector machine (SVM) and neural network (NN). The reported results indicated an accuracy of 86% in distinguishing lung cancer types, e.g., adenocarcinoma and squamous cell carcinoma [20]. Surprisingly, the reported results [21] in distinguishing non-small cell lung cancer adenocarcinomas from granulomas on non-contrast CT images showed that the developed CADx systems outperformed the radiologist readers. Joo et al. [22] developed a CADx system using an ANN for breast nodule malignancy diagnosis in US images. Their results demonstrated the potential to increase the specificity of US for characterization of breast lesions.

Overall, computer-aided diagnosis tool as a “second opinion” system could significantly enhance the radiologists’ performance by reducing the misdiagnosed rate of malignant cases, then decreases the false positive of the cases sent for surgical biopsy. Also with CADx, the diagnosis can be performed based on multimodality medical images in a non-invasive (without biopsy), fast (fast scanning) and a low-cost way (no additional examination cost).

2.1.3 Assessment and consultation

During the patient assessment phase, the radiation oncologist and patient meet to discuss the clinical situation. Circumstances like the risks and benefits of treatment and the patient’s goals of care are determined for the treatment strategy [14]. Useful information to assess the potential benefit of treatment is acquired, e.g., tumor

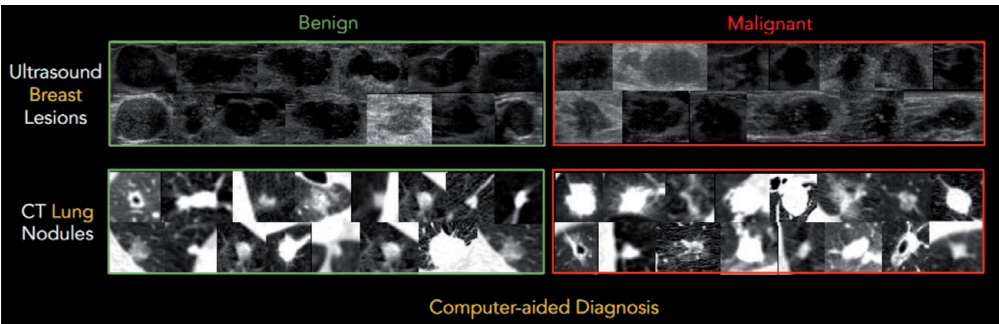


Figure 4. Computer-aided diagnosis for lung nodules and breast lesion with deep learning. It shows that it may be hard to differentiate for a person without a medical background and for a junior medical doctor (reproduced from [19]).

stage, prior and current therapies, margin status if post-resection, ability to tolerate multimodality therapy, and overall performance status [14]. Parameters that impact potential risk and tolerability of treatment are balanced, e.g., patient age, comorbidities, functional status, the proximity between tumor and critical normal tissues, and ability to cooperate with motion management [14]. All of these represent valuable features which can be utilized to build predictive models of treatment outcome and toxicity. These models, then, can be used to inform physicians and patients to manage expectations and guide trade-offs between risks and benefit [14].

Machine learning models [23–26] such as logistic regressions, decision trees, random forests, gradient boosting, and support vector machines are suitable for this purpose. Logistic regressions or decision trees are similarly effective [23, 24] for a goal to assist physicians and patients reach the best decision, compromising balance between interpretability of the results and accurate predictions. In case of accuracy is favored over interpretability, then methods [25, 26] such as random forests or gradient boosting, and SVMs with kernels, are better and consistently win most modeling competitions [14].

Overall, the delivery of models that could help with these scenarios require standardizing nomenclature and developing standards for data collection of these heterogeneous patient clinical data remain a challenge in radiation oncology.

2.2 Treatment simulation

Once a physician and patient have decided to proceed with radiation therapy, the physician will place robust instructions for a simulation, which is then scheduled. The order for simulation includes details about immobilization, scan range, treatment site, and other specifics necessary to complete the procedure appropriately [14]. Patient preparation for simulation could include fiducial placement, fasting or bladder/rectal filling instructions, or kidney function testing for intravenous (IV) contrast. Special instructions have given for patients with a cardiac device, or who are pregnant, and lift help or a translator is requested if necessary [14]. The treatment simulation process typically includes patient's setup and immobilization, three- or four-dimensional computed tomography (3DCT or 4DCT) image data acquisition, and image reconstruction/segmentation. Machine learning algorithms could have an essential role to play in this sequence to improve the simulation quality, hence a better treatment outcome.

2.2.1 3D/4DCT image acquisition

Three-dimensional CT anatomical image information for the patient are acquired during the simulation on a dedicated CT scanner ("CT-Simulator") to be used later for the treatment planning purposes. A good CT simulation is critical to the success of all subsequent processes, to achieve an accurate, high quality, robust, and deliverable plan for a patient. It could prevent a repeated CT simulation due to insufficient scan range, suboptimal immobilization, non-optimal bladder/rectal filling, artifacts, lack of breath-hold reproducibility, and so on [14]. 4DCT scanning is used increasingly in radiotherapy departments to track the motion of tumors in relation to the respiratory cycle of the patient. It monitors the breathing cycle of the patient and can either; acquire CT images at a certain point in the breathing cycle, or acquire CT images over the whole breathing cycle. This CT data is then used to generate an ITV (internal target volume) that encompasses the motion of the CTV (clinical target volume), or MIP (maximum intensity projection) scans to aid in the definition of an ITV [2]. 4DCT imaging is necessary for successful implementation of stereotactic ablative radiotherapy (SBRT), e.g., for early-stage NSCLC.

Few works [27–30] have carried out using ML-based methods for this purpose. For instance, a work by Fayad et al. [27] demonstrated an ML method based on the principal component analysis (PCA) to develop a global respiratory motion model capable of relating external patient surface motion to internal structure motion without the need for a patient-specific 4DCT acquisition. Its finding looks promising but future works of assessing the model extensively are needed. Another study by Steiner et al. [28] investigated an ML-based model on correlations and linear regressions for quantifying whether 4DCT or 4D CBCT (cone-beam CT) represents the actual motion range during treatment using Calypso (Varian Medical Systems Inc., Palo Alto, CA, USA) motion signals as the “ground truth.” The study results found that 4DCT and 4DCBCT under-predict intra-fraction lung target motion during radiotherapy. A third interesting one by Dick et al. [29] examined an ANN model for fiducial-less tracking for the radiotherapy of liver tumors through tracking lung-diaphragm border. The findings showed that the diaphragm and tracking volumes are closely related, and the method has indicated the potential to replace fiducial markers for clinical application. Finally, a study by Johansson et al. [30] investigated an ML-based PCA model for reconstructing breathing-compensated images showing the phases of gastrointestinal (GI) motion. Its results indicated that GI 4D MRIs could help define internal target volumes for treatment planning or support GI motion tracking during irradiation.

Overall, the discussed ML-based methods in the simulation area have shown the potential for improved accuracy of patient CT simulation. Machine learning utilization in 3D/4D CT image acquisition simulation is an area where the community has focused little effort. Thus, focusing on the simulation, there are many questions that could be answered/optimized through ML algorithms to aid in decision-making and overall workflow efficiency.

2.2.2 Image reconstruction

Here, we explore the power of machine learning based methods for image reconstruction in radiation oncology procedure. We present two application examples where ML has utilized for estimating CT from MRI images and reconstructing a 7 Tesla (7 T)-like MR image from a 3 T MR image.

The first application supports reconstructing an image modality from another imaging modality, e.g., CT image from MR image. Clinical implementation of MRI-only treatment planning radiotherapy approach requires a method to derive or reconstruct synthetic CT image from MR image. CT is currently supporting the workflows of radiation oncology treatment planning for dose calculations. However, CT imaging modality has some limitations in comparison with other modalities like MRI, e.g., (a) CT images provide poor soft tissue contrast compared to MRI scans which has superior visualization of anatomical structures and tumors, and (b) CT exposes radiation during CT imaging, which may cause side effect to the patient, where MRI is much safer and does not involve radiation.

Numerous studies [31–34] have demonstrated ML-based approaches to map CT images to MR images like deep learning (fully CNN) model [31], boosting-based sampling (RUSBoost) algorithm [32], random forest and auto-context model [33], and U-net CNN model [34]. Nie et al. [31] experimental results showed that deep learning method is accurate and robust for predicting CT image from MRI image. **Figure 5** shows the synthetic CT image from MRI data with deep learning and the “ground truth” MRI [31]. The developed deep learning model outperformed other state-of-the-art methods under comparison. Bayisa et al. [32] proposed an approach based on boosting algorithm indicated outperformance in CT estimation quality in comparison with the existing model-based methods on the brain and bone tissues.

Huynh et al. [33] experimental results showed that a structured random forest and auto-context based model can accurately predict CT images in various scenarios, and also outperformed two state-of-the-art methods. Chen et al. [34] investigated the feasibility of a deep CNN for MRI-based synthetic CT generation. The gamma analysis of their results with “ground truth” CT image for 1%/1 mm gamma pass rates was over 98.03%. The dosimetric accuracy on the dose-volume histogram (DVH) parameters discrepancy was less than 0.87% and the maximum point dose discrepancy within PTV (planning target volume) was less than 1.01% respect to the prescription on prostate intensity modulated radiotherapy (IMRT) planning.

Overall, the presented findings have obviously demonstrated the potential of the discussed methods to generate synthetic CT images to support the MR-only workflow of radiotherapy treatment planning and image guidance.

The second application supports reconstructing a high-quality image modality from a lower quality one, e.g., 7 T-like MR image from 3 T MR image. The advanced ultra—high 7 T magnetic field scanners provide MR images with higher resolution and better tissue contrast compared to routine 3 T MRI scanners. However, 7 T MRI scanners are currently more expensive, less available in clinical centers, and higher restrictions are required for safety due to its extremely high magnetic field power. As a result, generating/reconstructing a 7 T-like MR image from a 3 T MR image with ML-based approaches would resolve these concerns as well as facilitate early disease diagnosis.

Researchers [35–38] have developed ML-based models to generate a 7 T-like MR image from 3 T MR image. Approaches based on deep learning CNN [35], hierarchical reconstruction based on group sparsity in a novel multi-level canonical correlation analysis (CCA) space [36], and random forest and sparse representation [37, 38] have been investigated to map 3 T MR images to be as 7 T-like MR images. Bahrami et al. [35] visual and numerical results showed that deep learning method outperformed the comparison methods. **Figure 6** presents the reconstruction of 7 T-like MR image from 3 T MR image with deep learning. A second study [36] done by the same author showed that a hierarchical reconstruction based on group sparsity method outperformed other previous methods and resulted in higher accuracy in the segmentation of brain structures, compared to segmentation of 3 T MR images. Other studies by Bahrami et al. [37, 38] using random forest regression model and a group sparse representation showed that the predicted 7 T-like MR images can best match the “ground-truth” 7 T MR images, compared to other methods. Moreover, the experiment on brain tissue segmentation showed that predicted 7 T-like MR images lead to the highest accuracy in the segmentation, compared to segmentation of 3 T MR images.

Overall, the predicted 7 T-like MR images have demonstrated better spatial resolution compared to 3 T MR images. Moreover, delineation critical structure,

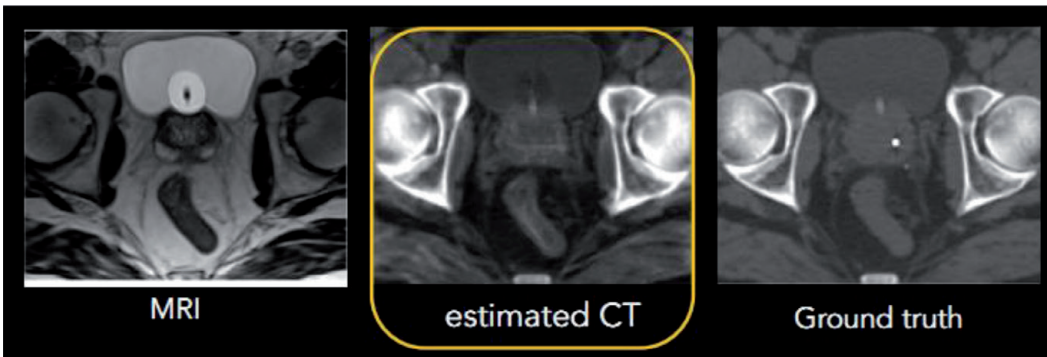


Figure 5. Synthetic CT image from MRI data. MR image (left), estimated CT form the MR (middle) with deep learning, and “ground truth” (right) MR image for the same subject (reproduced from [31]).

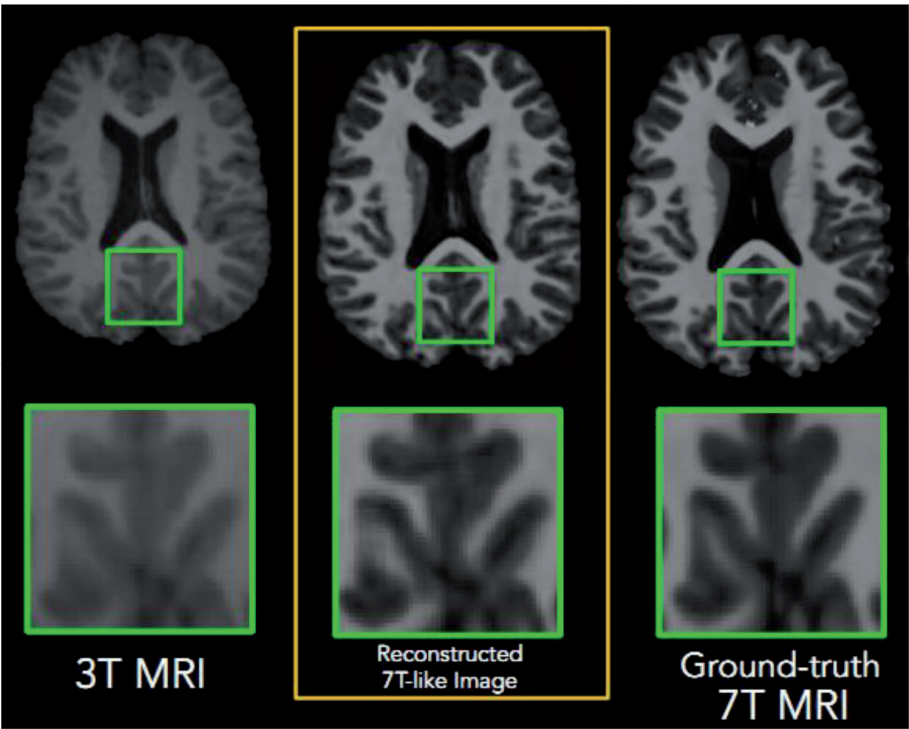


Figure 6. Reconstruction of 7 T-like MR image from 3 T MR image. 3 T MR image (left), reconstructed 7 T-like MR image (middle) using deep learning, and 7 T MR “ground truth” image (right) of the same subject with each one corresponded with a same selected zoomed area. From the figure, 7 T MR image shows clearly better anatomical details and tissue contrast compared to 3 T MR image (reproduced from [35]).

i.e., brain tissue structures on 7 T-like MR images showed better accuracy compared to segmentation of 3 T MR images. Adding to above, such high-quality 7 T-like MR image could better help disease diagnosis and intervention.

2.2.3 Image registration/fusion

Image registration in radiotherapy is the process of aligning images rigidly which allows some changes in images to be easily detected. However, such an alignment does not model changes from, e.g., organ deformation, patient weight loss, or tumor shrinkage. It is possible to take such changes into account using deformable image registration (DIR) which is a method for finding the mapping between points in one image and the corresponding points in another image. DIR has the perspective of being widely integrated into many different steps of the radiotherapy process. The tasks of planning, delivery, and evaluation of radiotherapy can all be improved by taking organ deformation into account. Use of image registration in image-guided radiotherapy (IGRT) can be split into intra-patient (*inter- and intra-fractionated*) and inter-patient registration. Intra-patient registration is matching of images of a single patient, e.g., *inter-fractional registration* (i.e., improving patient positioning, and evaluating organ motion relative to bones) and *intra-fractional registration* (i.e., online tracking of organ movement). In contrast, inter-patient registration is matching images from different patients (i.e., an “average” of images acquired from a number of patients, thereby allowing information to be transferred from the atlas to the newly acquired image). The process of combining information from two images after these have been registered is called data fusion. A particular use of data transfer between images is the propagation of contours from the planning image or an atlas to a newly acquired image [39, 40]. Although many image registration methods have been proposed, there are still some challenges for DIR of complex situations, e.g., large anatomical changes and dynamic appearance changes.

Advancement in computer vision and deep learning could provide solutions to overcome these challenges of conventional rigid/deformable image registrations.

Various machine learning-based methods [41–47] for image registration have proposed by investigators to not only align the anatomical structures but also alleviate the appearance difference. Hu et al. [41] proposed a method based on regression forest for image registration of two arbitrary MR images. The learning-based registration method achieved higher registration accuracy compared with other counterpart registration methods. Zagoruyko et al. [42] proposed a general similarity function for comparing image patches, which is a task for many computer vision problems. The results showed that such an approach like CNN-based model can significantly outperform other state-of-the-art methods. Jiang et al. [43] employed a discriminative local derivative pattern method to achieve fast and robust multi-modal image registration. The results revealed that the proposed method can achieve superior performance regarding accuracy in multimodal image registration as well as also indicated the potential for clinical US-guided intervention. Neylon et al. [44] developed a deep neural network for automated quantification of DIR performance. Their results showed a correlation between the NN predicted error and the “ground truth” for the PTV and the organs at risk (OARs) were consistently observed to be greater than 0.90. Wu et al. [45, 46] developed an NN-based registration quality evaluator, and a deep learning-based image registration framework, respectively, to improve the image registration robustness. The quality evaluator method [45] showed potentials to be used in a 2D/3D rigid image registration system to improve the overall robustness, and the new image registration framework [46] consistently demonstrated more accurate registration results when compared to the state-of-the-art. Kearney et al. [47] developed a deep unsupervised learning strategy for CBCT to CT deformable image registration. The results indicated that deep learning method performed better than rigid registration, intensity corrected demons and landmark-guided deformable image registration for all evaluation metrics.

Overall, most of the machine learning based methods discussed here for image registration have revealed superior performance regarding accuracy in multimodal image registration. Hence, potentials for improved rigid/deformable image registration in radiation oncology are clinically feasible.

2.2.4 Image segmentation/auto-contouring

Volume definition is a prerequisite for meaningful 3D treatment planning and for accurate dose reporting. International Commission on Radiation Units and Measurements (ICRU) Reports No. 50, 62, 71 and 83 [48] define and describe target volumes (e.g., planning target volume) and critical structure/normal tissue (organ at risk) volumes that aid in the treatment planning process and that provide a basis for comparison of treatment outcomes. The organ at risk is an organ whose sensitivity to radiation is such that the dose received from a treatment plan may be significant compared with its tolerance, possibly needs to be delineated to evaluate its received dose [49]. Multimodal diagnostic images, e.g., CT, MRI, US, positron emission tomography (PET)/CT, etc. can be used through image fusion to help in the process of delineating tumor and OAR structures on CT slices acquired during the patient’s treatment simulation. The delineation (auto-contouring) process has subsequently become performed via automated or semi-automated analytical model-based software commercially available for clinical use (e.g., Atlas based-models). These software tools are performing reasonably well for critical organs/OARs delineation but not yet ready for tumor/target structures contouring which represent a challenging task. State-of-the-art machine learning algorithms may play an effective role here for both tasks.

Several ML-based methods [52–58] have reported for tumor/target segmentation/auto-contouring, e.g., brain [52–55], prostate [56], rectum [57], sclerosis lesion [58], etc. The reported results showed that deep learning [54, 55] and ensemble learning [50, 53] ML-based methods are the winner algorithms over the other ML-based methods in the brain tumor segmentation competitions [50]. Such a method by Osman [52] based on SVM for glioma brain tumor segmentation showed a robust consistency performance on the training and new “unseen” testing data even though its reported accuracy on multi-institution datasets was reasonably acceptable. **Figure 7** shows the whole glioma brain tumor segmentation on MRI (BRATS’2017 dataset [50, 51]) with an SVM model [52]. For organs segmentation, deep learning algorithm [57, 59, 60] has shown a superior performance than other state-of-the-art segmentation methods and commercially available software for segmentation of, e.g., rectum [57], parotid [59], etc.

Overall, tumor/target segmentation/auto-contouring using ML-based methods still remains challenging for some reasons such as availability of big data of multi-modal images with their “ground truth” annotation data for training these models. Recent advances in computer vision, specifically around deep learning [61], are particularly well suited for segmentation and it has shown superiority over the other machine learning algorithms for tumor and organs segmentation tasks.

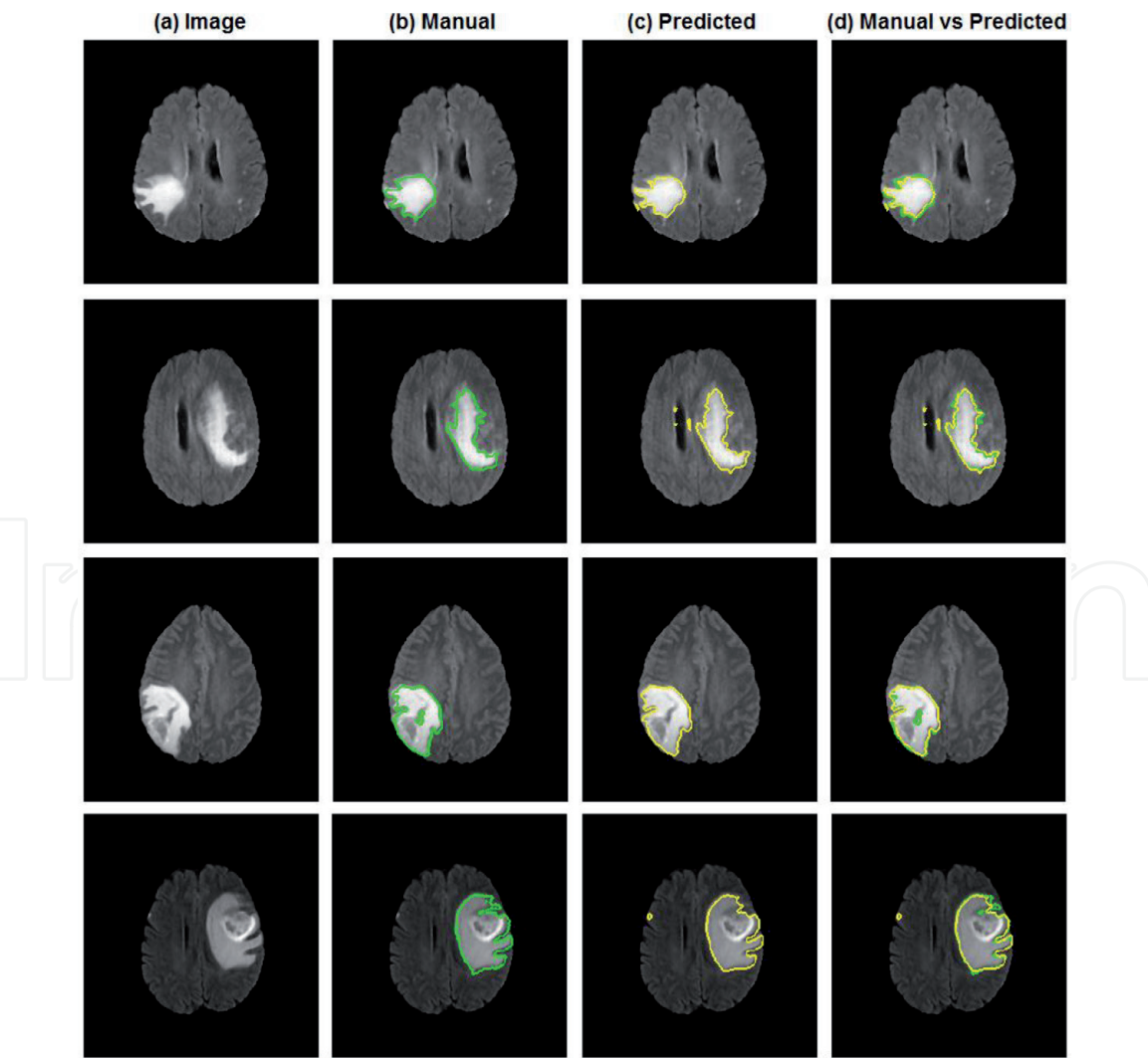


Figure 7. Whole glioma brain tumor segmentation on MRI (BRATS’2017 dataset [50, 51]). (a) T2-FLAIR MRI, (b) manual “ground truth” glioma segmentation by an experienced board-certified radiation oncologist, (c) machine learning—SVM model glioma segmentation [52], and (d) both, manual and ML, segmented annotations overlap; for four different subjects.

2.3 Treatment planning

The planning process starts by delineating both the target(s) and the OARs as we discussed it earlier in the image segmentation section (Section 2.2.4). Once the target volumes and OARs have been outlined/contoured, the planning process continues by (1) setting dosimetric goals for targets and normal tissues; (2) selecting an appropriate treatment technique (e.g., 3D, fixed beam IMRT, VMAT (volumetric arc radiation therapy), protons); (3) iteratively modifying the beams/weights/etc., until the planning goals have been achieved; and (4) evaluating (estimating the treatment dose distributions with prescribed doses in the treatment planning system using dose calculation algorithms) and approving the plan [14]. The applications of machine learning in radiotherapy treatment planning as a tool for knowledge-based treatment planning (KBTP) and automated/self-driven planning process will be discussed in this section.

2.3.1 Knowledge-based treatment planning

Prior information about patient status and previously archived treatment plans, particularly if performed by expert medical dosimetrists/physicists, could be used to inform the treating team of a currently pending case [2]. This concept of using prior treatment planning information constitutes the underlying principle of the so-called knowledge-based treatment planning. Such KBTP approaches have leveraged hundreds of prior treatment plans to reproducibly improve planning efficiency across multiple disease sites [62]. **Figure 8** illustrates the schematic of a KBTP System [2]. The motivation for KBTP approach lies in reducing current complexity and time spent on generating a new treatment plan from each incoming patient, as well as its potential for decision-making support in radiotherapy.

Several studies [63–67] have carried out to explore the utilization of KBTP approach for treatment plan generation in radiotherapy. The current scientific research and available commercial products for KBTP are limited to predicting DVHs within accepted ranges [14]. Plans generated based on KBTP utilizing artificial intelligence often meet or exceed adherence to dose constraints compared to manually generated plans in many clinical scenarios (e.g., prostate cancer [63], cervical cancer [64], gliomas and meningiomas [65], head and neck cancer [66], and spine SBRT [67]). A more recent commercial product, Quick Match

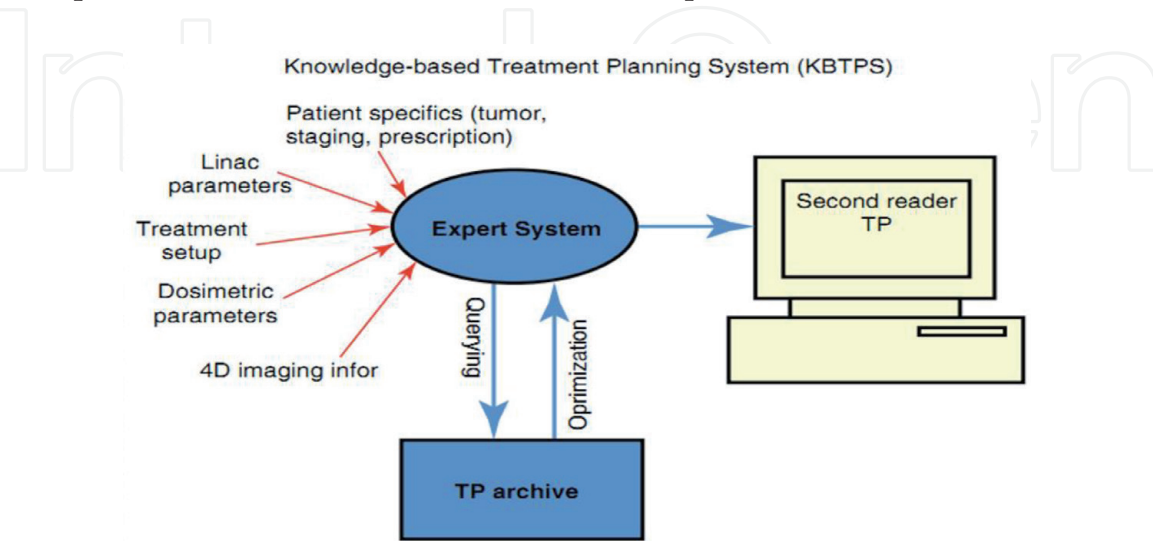


Figure 8. Schematic of a KBTP system. Initially, the user builds a query using features related to patient, disease, imaging, treatment setup, dose, etc., for the treatment plan (TP). Then, the database returns a set of similar treatment plans that the user could select from to optimize and compare with the current one according to the query (reproduced from [2]).

(Siris Medical, Redwood City, CA, USA), uses gradient boosting (the most accurate algorithm on expectation when structured data are available) to explore predictions in dosimetric trade-offs [68]. This application provides quick rough predicted treatment planning results to be obtained before the treatment planning process. Thus it can facilitate communication between dosimetrist and physicians, establish individualized and achievable goals, and help physicians and patients decide the course of a plan before initializing the treatment planning process. For example, it can help to choose an optimal technique (e.g., photon versus protons). This approach has also been applied to post-planning quality assurance of DVH data [69, 70].

Overall, the incentive for such an approach like KBTP lies in reducing current complexity and time spent on generating a new treatment plan from each incoming patient. It is believed that such a standardization process based on KBTP can help enhance consistency, efficiency, and plan quality. Ultimately, data-driven planning is not fully automated at present as it requires expert oversight and/or intervention to ensure safely deliverable treatment plans.

2.3.2 Automated planning (self-driving) process

Once the dosimetric goals have been established and the technique chosen, automatic plan generation is also possible [14].

Some attempts [71, 72] have made to solve various aspects of this problem by predicting the best beam orientations. The larger task of automated treatment planning, however, is well suited for reinforcement learning method [14]. Reinforcement is extensively used in games, self-driving cars, and other popular-culture applications. In reinforcement learning method, an algorithm learns to navigate a set of rules, given some constraints, by self-correcting its decisions. Basically, the algorithm will take a decision (for instance, increase the weight of a given constraint) and learn from the simulator (the treatment planning system) whether the decision resulted in the right direction [14]. This technique has successfully used by Google Brain to develop an algorithm capable of beating a Go world champion [73]. So, reinforcement technique could provide performance at the level of our best dosimetrists if properly implemented.

Overall, one challenge of achieving full automatic planning using reinforcement learning lies in the close integration and need for robust treatment planning systems (TPSs) [14]. The future vision is toward a fully-automated planning process, from contouring to plan creation [62], with the human experts (dosimetrists, physicists, and physicians) evaluating, supervising, and providing QA to the given results.

2.4 Quality assurance and treatment delivery

Quality assurance (QA) is demanding for the safe delivery of radiotherapy. It represents a core part of a medical physicist's task in the clinical practice. Machine learning could be utilized to solve multiple long-standing problems and improve workflow efficiency. Its applications in the quality assurance (e.g., detection and prediction of radiotherapy errors, and treatment planning QA) and treatment delivery validation (e.g., prediction planning deviations from the initial intentions, and prediction the need for re-planning for adaptive radiotherapy) are discussed in this section.

2.4.1 Quality assurance

Machine learning has potential in many aspects of radiotherapy QA program, specifically in error detection and prevention, treatment machine QA, patient-specific quality assurance, etc. In addition, ML may contribute to automating the

QA process and analysis, which significantly influence an increase in efficiency and a decrease in the physical effort in performing the QA.

Numerous studies [74–77, 79–83] have conducted to develop a computerized system for QA process based on machine learning methods. We can generally categorize these QA into the machine-based and patient-based approach. For machine-based QA approach, ML utilizations for automatic QA process of medical linear accelerator (Linac) machine [74–77] have investigated by research scientists. A study by Li et al. [74] investigated the application of ANN to monitor the performance of the Linac for continuous improvement of patient safety and quality of care. The preliminary results showed better accuracy and effective applicability in the dosimetry and QA field over other techniques, and in some cases, its performance beat the detection rate by current clinical metrics. El Naqa et al. [75] introduced a system utilizing anomaly detection to overcome the problem of direct modeling of QA errors and rare events in radiotherapy and to support the intent of automated QA and safety management for patients undergo radiotherapy treatment. Ford et al. [76] and Hoisak et al. [77] investigated quantifying the error-detection effectiveness of commonly used quality control (QC) measures [76] preventative maintenance [77] in radiation oncology. The results indicated that the effectiveness of QC measures in radiation oncology depends sensitively on which checks are used and in which combinations [76], and also a decreased machine downtime and other technical failures leading to treatment cancellations [77]. The ability of these ML algorithms to automatically detect outliers allows physicists to focus attention on those aspects of a process most likely to impact the patient care, as recommended in AAPM Task Group report 100 [78].

For patient-based QA approach, application of ML algorithms for a plan and patient-specific QA, multi-leaf collimators (MLCs) QA, and imaging [79–83] have discovered by many investigators. A study by Valdes et al. [80] investigated the use of SVM-based system to automatically detect problems with the Linac 2D/3D imaging system that are used for patient IGRT treatment accuracy. The proposed method results showed that the bare minimum and the best practice QA programs could be implemented with the same manpower. Regarding plan QA and patient-specific QA, investigators [81, 82] studied applications of Poisson regression with LASSO regularization to predict individualized IMRT QA passing rates. Their results pointed out that virtual IMRT QA can predict passing rates with a high likelihood, allows the detection of failures due to setup errors. Osman et al. [79] and Carlson et al. [83] utilized NN and a cubist algorithm, respectively, to predict MLC positional errors using the Linac generated log file data of IMRT and VMAT delivered plans. Their studies results showed that predicted parameters were in closer agreement to the delivered parameters than the planned parameters. The inclusion of these predicted deviations in leaves positioning into the TPS during dose calculation leads to a more realistic representation of plan delivery. **Figure 9** illustrates a generic flow diagram and results of an NN utilized for prediction of MLCs positional errors [79].

Overall, despite these significant improvements in QA processes with the involvement of ML, they carry implicit maintenance costs in the form of additional QA demands for the algorithms themselves. The performance of all deployed ML-based algorithms will, therefore, need to be verified periodically using an evolving series of tests [62]. Virtual QA can have profound implications on the current IMRT/VMAT process and potentially enabling intelligent resource allocation in favor of plans more likely to fail.

2.4.2 Treatment delivery

Tumor shrinkage and anatomical patient variations (e.g., due to weight loss) may occur throughout a few weeks of a fractionated radiotherapy treatment. Adaptive

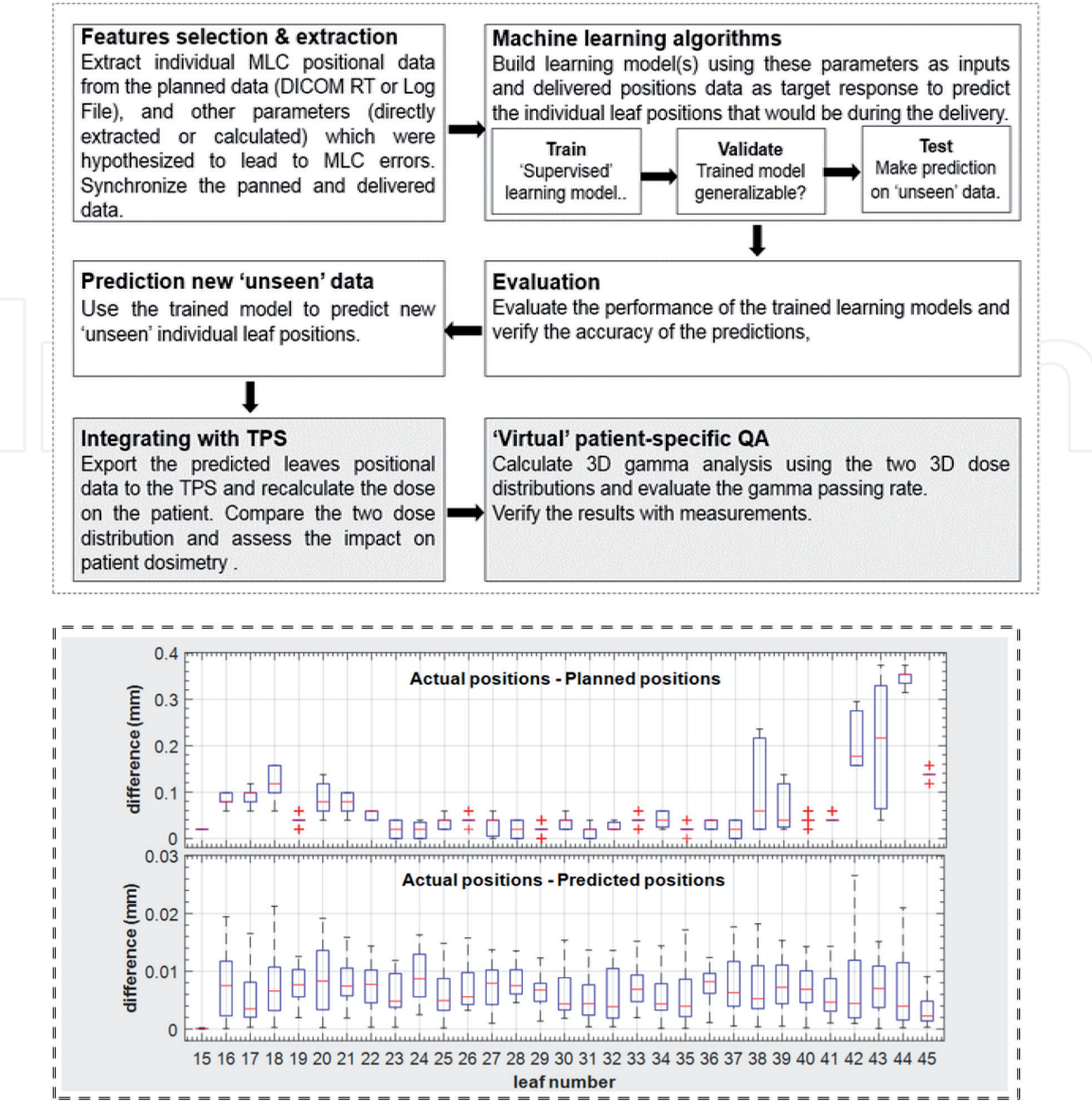


Figure 9.
Top: A generic flow diagram of the proposed method of prediction MLC positional errors [79]. Bottom: Differences in the leaf positions between the delivered and planned (upper), and delivered and predicted with NN (lower). Boxes report quartiles including the median (the 50% central sample distribution); whiskers and dots indicate outliers.

radiation therapy (ART) is a treatment approach that uses frequent imaging to compensate for anatomical differences that occur during the course of treatment. Images are taken daily, or almost daily. When significant changes are observed, replanning is considered. It is possible to achieve image-guided adaptation either off-line (i.e., using image information acquired during a fraction for improving following fraction) or online (i.e., changing treatment plan for a fraction based on information from the same fraction).

The re-planning process involves three steps [84]: (1) simulating the plan from the daily CBCT image dataset to calculate the estimated actual delivered daily dose for the given treatment fraction, (2) delineating the structures of interest to obtain daily DVHs to provide dose metrics for the tumor and OARs from which radiation oncologists can evaluate treatment plan effectiveness, and (3) modifying the doses to the therapeutic target and OARs to meet the dose constraints in the original treatment plan. The implementation of adaptive radiotherapy into routine clinical practice is technically challenging and requires significant resources to perform and validate each process step. It needs to be fast (where time is a big issue) in order to fit into the clinical workflow. Machine learning techniques, i.e., deep learning, may offer potentials to have very sophisticated software tools for adaptive therapy. In recent years, deep learning [61] applications have grown in a variety of fields including video games, computer vision, and pattern recognition.

A number of researchers [85–88] have investigated the application of ML, particularly deep learning, in treatment re-planning process for adaptive radiotherapy. Studies by Guidi et al. [85] and Chetvertkov et al. [86] conducted to predict patients who would benefit from ART and re-planning intervention using SVM [85] and PCA [86] ML models. The studies results indicated a capability of identifying patients would benefit from ART and ideal time for a re-planning intervention. Tseng et al. [87] investigated deep reinforcement learning based on historical treatment plans for developing automated radiation adaptation protocols for lung cancer patients aiming to maximize tumor local control at reduced rates of radiation pneumonitis. The study findings revealed that automated dose adaptation by deep reinforcement learning is a feasible and promising approach for achieving similar results to those chosen by clinicians. Varfalvy et al. [88] introduced a new automated patient classification method based on relative gamma analysis and hidden Markov models to identify patients undergoing important anatomical changes during radiotherapy. The results obtained indicated that it can complement the clinical information collected during treatment and help identify patients in need of a plan adaptation.

Overall, adaptive radiotherapy demands a high-speed planning system, combined with high-quality imaging. Deep learning-based ML methods have shown potential and feasibility to transform adaptive radiation therapy more effectively and efficiently into the routine clinical practice soon. Effective implementation of adaptive radiation therapy can further improve the precision in the radiotherapy treatments.

2.5 Patient follow-up

Patient follow-up begins at the start of the treatment and continues to beyond the end of the treatment. Accurate prediction of treatment outcomes would provide clinicians with better tools for informed decision-making about expected benefits versus anticipated risks [2]. Machine learning has the potential to revolutionize the way radiation oncologists follow patients treated with definitive radiation therapy [14]. In addition, it may potentially enable practical use of precision medicine in radiation oncology by predicting treatment outcomes for individual patients using radiomics “tumor/healthy tissue phenotypes” analysis.

2.5.1 Treatment outcome

Radiotherapy treatment outcomes are determined by complex interactions among treatment, anatomical, and patient-related variables [2]. A key component of radiation oncology research is to predict at the time of treatment planning, or during the course of fractionated radiation treatment, the tumor control probability (TCP) and normal tissue control probability (NTCP) for the type of treatment being considered for that particular patient [2]. Recent approaches have utilized increasingly data-driven models incorporating advanced bioinformatics and machine learning tools in which dose-volume metrics are mixed with other patients- or disease-based prognostic factors in order to improve outcomes prediction [2]. Obviously, better models based on early assessment are needed to predict the outcome, in time for treatment intensification with additional radiotherapy, early addition of systemic therapy, or application of a different treatment modality [14].

Many research scientists [89–95] have investigated the application of ML in radiotherapy treatment response and outcome predictions. Lee et al. [89] studied utilizing of Bayesian network ensemble to predict radiation pneumonitis risk for NSCLC patients whom received curative 3D conformal radiotherapy. The preliminary results demonstrated that such framework combined with an ensemble method can possibly improve the prediction of radiation pneumonitis under real-life clinical circumstances.

Naqa et al. [90] introduced a data mining framework estimating model parameters for predicting TCP using statistical resampling and a logistic, SVM, logistic regression, Poisson-based TCP, and cell kill equivalent uniform dose model. Their findings indicated that prediction of treatment response can be improved by utilizing data mining approaches, which were able to unravel important non-linear complex interactions among model variables and have the capacity to predict on unseen data for prospective clinical applications. Zhen et al. [91] introduced a CNN model to analyze the rectum dose distribution and predict rectum toxicity. The evaluation results demonstrated the feasibility of building a CNN-based rectum dose-toxicity prediction model with transfer learning for cervical cancer radiotherapy. Deist et al. [92] studied the comparison of six ML classifiers (namely, decision tree, random forest, NN, SVM, elastic net logistic regression, and LogitBoost) for chemo-radiotherapy to estimate their average discriminative performance for radiation treatment outcome prediction. The study results indicated that random forest and elastic net logistic regression yield higher discriminative performance in (chemo) radiotherapy outcome and toxicity prediction than other studied classifiers. Yahya et al. [93] explored multiple statistical-learning strategies for prediction of urinary symptoms following external beam radiotherapy of the prostate. The study results showed that logistic regression and multivariate adaptive regression splines (MARS) were most likely to be the best-performing strategy for the prediction of urinary symptoms. Zhang et al. [94] studied the prediction of organ-at-risk complications as a function of dose-volume constraint settings using SVMs and decisions trees. Their results showed that ML can be used for predicting OAR complications during treatment planning allowing for alternative dose-volume constraint settings to be assessed within the IMRT planning framework. A review by Kang et al. [95] presented the use of ML to predict radiation therapy outcomes from the clinician's point of view. The study focused on three popular ML methods: logistic regression, SVM, and ANN. The study concluded that although current studies are in exploratory stages, the overall methodology has progressively matured, and the field is ready for larger-scale further investigation.

Overall, a significant hope of advanced clinical informatics systems would be the potential to learn even more about the safety and effectiveness of the therapies that are provided to patients. The rapid adoption of technological advancements in radiotherapy has made outcomes analyses of both treatment regimens and the systems that deliver them to be separated substantially in time. Successful application of advanced ML tools for radiation oncology big data is essential to better-predicting radiotherapy treatment response and outcomes. The ultimate measure of success is an improvement in outcomes which can manifest as decreased toxicity or increased tumor control.

2.5.2 Radiomics for “precision medicine” radiotherapy

Precision medicine is a treatment strategy for making decisions about a molecularly targeted agent according to genetic mutations, rather than affected organs. Radiomics is the comprehensive quantitative analysis of medical images in order to extract a large number of phenotypic features (including those based on size and shape, image intensity, texture, relationships between voxels, and fractal characteristics) reflecting cancer traits or phenotypes. Then it explores the associations between the features and patients' prognoses in order to improve decision-making at each radiation treatment step (diagnosis, treatment planning, treatment delivery, and follow-up) and hence precision medicine in radiotherapy [96]. Individual patients can be stratified into subtypes based on radiomic biomarkers that contain information about cancer traits that determine the patient's prognosis [97]. Machine-learning algorithms can then be deployed to correlate the computer-extracted image-based

features in radiomics with biological observations or clinical outcomes. Here, we present some current results and emerging paradigms in radiomics boosted with ML approaches in clinical radiation oncology (recently received higher attention from the investigators) to maximize its potential impact on precision radiotherapy.

Several research scientists [97–102] have investigated the using of ML methods for predicting radiotherapy outcomes (e.g., survival, treatment failure or recurrence, toxicity or developed a late complication, etc.) using radiomics features to improve decision-making for precision medicine. A review study by Arimura et al. [97] showed that radiomic approaches in combination with AI may potentially enable the practical use of precision medicine in radiation therapy by predicting outcomes and toxicity for individual patients. Aerts et al. [98] performed a radiomic analysis of 440 features quantifying tumor image intensity, shape, and texture, which are extracted from CT data of patients with lung or head-and-neck cancer. The study findings proved the power of radiomics for identifying a general prognostic phenotype existing in both lung and head-and-neck cancer. **Figure 10** shows a workflow of radiomics analysis (example: CT radiomic analysis of with lung cancer) [98]. A study by Depeursinge et al. [99] investigated the importance of pre-surgical CT intensity and texture information from ground-glass opacities and solid nodule components for the prediction of adenocarcinoma recurrence in the lung using LASSO and SVMs, and their survival counterparts: Cox-LASSO and survival SVMs. The study results showed the usefulness of the method in clinical practice to identify patients for which no recurrence is expected with very high confidence using a pre-surgical CT scan only. Lambin et al. [100] studied the development of automated and reproducible analysis methodologies to extract more information from image-based features. The study addressed the radiomics as one of the approaches that hold great promises but need further validation in multi-centric settings. A review by Wu et al. [101] recommended that ultimately prospective validation in multi-center clinical trials will be needed to demonstrate the clinical validity and utility of newly identified imaging markers and truly establish the value of radiomics and radiogenomics in precision radiotherapy. Lao et al. [102] investigated if deep features extracted via transfer learning can generate radiomics signatures for prediction of overall survival in patients with glioblastoma multiforme using the LASSO Cox regression model. The study outcomes demonstrated that the proposed method is capable to generate prognostic imaging signature for OS prediction

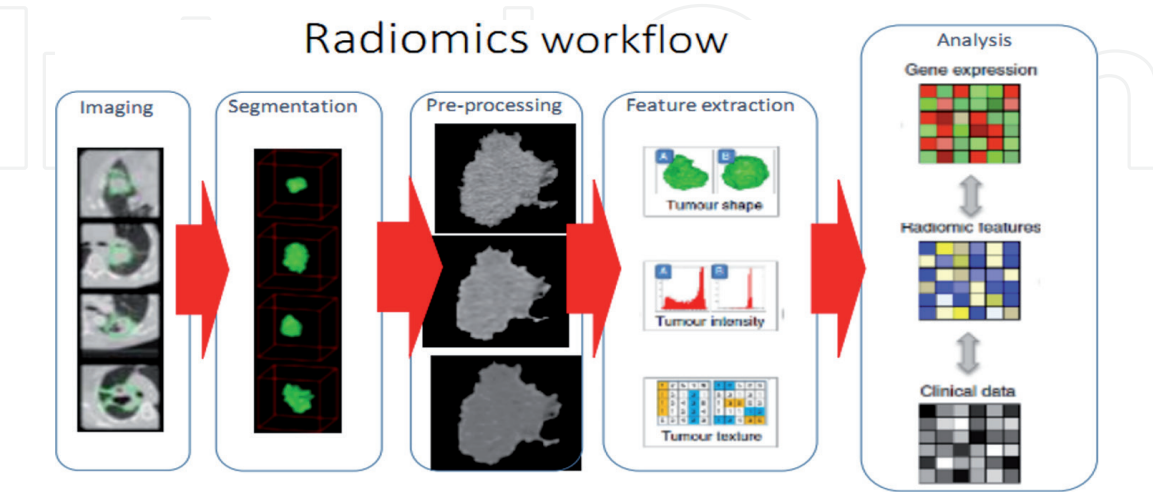


Figure 10. A typical radiomics workflow. *Imaging:* Tumors are different. Example CT images with tumor contours of lung cancer patients. *Segmentation:* 3D visualizations of tumor contours delineated by experienced physicians on all CT slices. *Pre-processing:* Strategy for extracting radiomics data from images. *Feature Extraction:* Features are extracted from the defined tumor contours on the CT images quantifying tumor intensity, shape, texture and wavelet texture. *Analysis:* For the analysis, the radiomics features are compared with clinical data and gene-expression data (reproduced from [98]).

and patient stratification for glioblastoma, indicating the potential of deep imaging feature-based biomarker in preoperative care of glioblastoma patients.

Overall, radiomics is the study of imaging data from any imaging source that is used to predict the therapeutic outcome, as well as radiogenomics. The limited reproducibility of imaging systems both within and across institutions remains a significant challenge for radiomics [98, 100]. Application of deep learning to image quantification has produced stellar results in other areas [103] which can be transferred into the radiomics analysis. Physicians may prescribe a more or less intense radiation regimen for an individual based on model predictions of local control benefit and toxicity risk [2], which would be considered for the optimal treatment planning design process and hence improving the quality of life for radiotherapy cancer patients. Also, as imaging is routinely used in clinical practice, radiomics is providing an unprecedented opportunity to improve decision-making support toward precision medicine in cancer treatment at low cost.

3. Discussion

A comprehensive review of the most recent evolution and ongoing research utilizing machine learning methods in radiation oncology in the era of big data for precision medicine has been provided in this chapter and critically discussed.

3.1 Big data in radiation oncology: challenges?

There are ongoing community-wide efforts in term of big data in radiation oncology, e.g., [9, 10, 50, 51] have made available and established validation frameworks [50] used as a benchmark for the evaluation of different algorithms. Deep learning [61] based models have indicated superiority among the other alternatives for the most prediction tasks in radiation oncology. However, it requires a lot of annotated datasets (across multiple institutions) to tune the algorithm (even when transfer learning is used [14]) to obtain high prediction accuracy. This can prove challenging in radiation oncology, where datasets are limited. Standardizing the radiation oncology nomenclature (i.e., clinical, dosimetric, imaging, etc.), which is aided by the AAPM task group TG-263 efforts [104], and developing standards for data collection process (structures) of the patient data are also essential for training models using datasets from multiple institutions.

3.2 What are the strengths and limitations of ML algorithms applied?

There is no one algorithm works best for every problem (“No Free Lunch”). Each ML algorithm has its strengths and limitations. **Table 1** lists the strengths and weaknesses of the most machine learning methods discussed here appearing in radiation oncology studies. It is believed that such usage optimization of these models with available resources would provide improved solutions. A major limitation in the acceptance of ML by the larger medical community has been addressed as the “black box” stigma, where the ML algorithm maps a given input data to output predictions without providing any additional insight into the system mapping [6]. Interpretability of algorithms used (e.g., the ability for humans experts to understand the reasons behind a prediction) will play an important role to avoid preventable errors. Although there are inherently interpretable ML algorithms, for instance, decision trees, Bayesian networks, or generalized linear models (e.g., logistic regression), they are usually outperformed in terms of accuracy by ensemble methods or deep neural networks (not interpretable and provide very

| Method | Strengths | Weaknesses |
|--|--|---|
| Decision tree | Interpretability (with a format consistent with many clinical pathways) | Overgrowing a tree with too few observations at leaf nodes |
| Random forest | Often can produce very accurate predictions with little feature engineering | Not easily interpretable, and not optimizing the number of trees |
| LASSO regression | Better interpretability (compared to ridge regularization method) | Provides a bias towards zero (not be appropriate in some applications) |
| Gradient boosting machines | Generates very stable results (compared to random forest) | More tuning parameters (compared to random forest), and overfitting |
| Support vector machines | Very accurate, few parameters that require tuning, and kernels options | Not readily interpretable, and not optimizing the parameters perfectly |
| Neural networks or more precisely artificial neural networks | Works even if one or a few units fail to respond to the network | Referred to as “black box” models and provide very little insight, and require a large diversity of training datasets |
| Deep learning | Very accurate, can be adapted to many types of problems, and the hidden layers reduce the need for feature engineering | Requires a very large amount of data, and computationally intensive to train |
| Logistic regression | Have a nice probabilistic interpretation, and updated easily with new data | Not flexible enough to naturally capture more complex relationships |
| K-means | Fast, simple, and flexible | Manually specify the number of clusters |
| Ensembles (decision tree) | Perform very well, robust to outliers, and scalable | Unconstrained, and prone to overfitting |
| Principal component analysis | Versatile, fast, and simple to implement | Not interpretable, and manually set a threshold for a cumulative variance |
| Naive Bayes | Performs surprisingly well, easy to implement, and can scale with the dataset | Often beaten by models properly trained and tuned (algorithms listed) |

Table 1.
Strengths and weaknesses of the most machine learning methods discussed here appearing in radiation oncology studies.

little insight) for large datasets [6, 13]. The development of accurate and interpretable models using different ML architectures is an active area of research [6]. As with any algorithm that we use in radiation oncology today (e.g., dose calculation or deformable registration), ML algorithms will need acceptance, commissioning, and QA to ensure that the right algorithm or model are applied to the right application and that the model results make sense in a given clinical situation. Finally, the field of radiation oncology is highly algorithmic and data-centric, and while the road ahead is filled with potholes, the destination holds tremendous promise [14].

3.3 How far are the reported results by the investigators correct?

The reported prediction results [15–38, 41–47, 52–60, 63–67, 71, 72, 74–77, 79–83, 85–88, 89–95, 97–102] by investigators indicate the performance of these predictive models on data that used in modeling. However, these ML models can suffer from different data biases which may lead to lack of generalizability. A machine learning system trained on local datasets only may not be able to predict (reproduce) the needs of out-of-sample datasets (new datasets that are not presented in the training data). External validation of models in cohorts, which were acquired independently from the discovery cohort (e.g., from another institution) is considered the gold standard for true estimates of performance and generalizability of prediction models [6]. The application of different algorithms to the same dataset may yield variable results for predictors found to be significantly associated with the outcome of interest [6, 105]. However, this may

also suggest a potential limitation of self-critical assessment of published ML models or realistic confidence levels with implications for their practical clinical value [6].

3.4 How would the reported results be improved?

Although promising and improving accuracy results of many ML-based predictive models in radiation oncology have been reported [18, 19, 21, 31–38, 41–43, 53–55, 74, 79–83, 85, 86, 89–95, 97–102], the effective applications of these methods in day-to-day clinical practice are very few yet. Such an example of a recently deployed commercial product into clinical use is Quick Match (Siris Medical, Redwood City, CA, USA) [68]. A private initiative, such as IBM's Watson, is already used in some institutions such as the Memorial Sloan Kettering Cancer Center in New York [106–109]. Watson Oncology [108] is a cognitive AI computing system designed to support the broader oncology community of physicians as they consider treatment options with their patients. To improve the prediction accuracy of these reported results, more training and validation datasets from multi-institution are required. Such frameworks, e.g., [50] to compare these methods on standard consensus data to establish benchmarks for evaluating different models would definitely lead to improving these results and developing robust toolkits/systems. It is anticipated to see ML and AI tools very soon settled more effectively with the indispensable role in the routine clinical practice for the benefit of patients, society, and the profession.

3.5 Impact on automating the clinical process

The machine learning systems have been developed and deployed to do jobs on their own. Automated clinical processes in radiation oncology could be auto-piloted with driving technologies to execute automated tasks. For example, data-driven planning [63–67] is not fully automated at present as it requires expert oversight and/or intervention to ensure safely deliverable treatment plans. One challenge of achieving full automatic planning using reinforcement learning lies in the close integration and need for robust TPSs [14]. The future vision is toward a fully-automated planning process, from contouring to plan creation. Machine-based and patient-based virtual QA can have profound implications on the current IMRT/VMAT process. The automated process nature would definitely lead to expediting radiation oncology workflow and reduce the time burden of human intervention [62].

3.6 Impact on clinical decision-making support toward precision medicine in radiation oncology

ML tools for computer-aided detection/diagnosis [15–22] as “second opinion” systems for clinical decision-making support would undoubtedly enhance the radiologists' performance and hence improved diagnostic performance. The emerging paradigms in radiomics for therapeutic outcome predictions (i.e., patient's survival, decrease recurrence, late complication, etc.) [97–102] for individual patients would maximize its potential impact on precision radiotherapy. Individual patients can be stratified into subtypes based on radiomic biomarkers that contain information about cancer traits that determine the patient's prognosis [97]. Therefore, physicians may prescribe a more or less intense radiation regimen for an individual based on model predictions of local control benefit and toxicity risk [2], which would be considered for the optimal treatment planning design process and hence improving the quality of life for radiotherapy cancer patients. Effective implementation of adaptive radiation therapy with ML [85–88] can also further improve the precision in the radiotherapy treatments. The pre-planning prediction of dosimetric tradeoffs to assist physicians and patients

to make better informed decisions about treatment modality and dose prescription [68] thus it can establish individualized and achievable goals. The clinical implications derived from personalized cancer therapy ensure not only that patients receive optimal treatment, but also that the right resources are being used for the right patients.

4. Conclusions

Machine learning methods used in radiation oncology workflow, from patient consult to follow-up, are presented and discussed in this chapter. Big data in radiation oncology, efforts made and current challenges, are addressed. With the era of big data, the utilization of machine learning algorithms in radiation oncology is growing fast. ML techniques could compensate for human limitations in handling a large amount of flowing information in an efficient manner, in which simple errors can make the difference between life and death. Machine learning is also indispensable in the radiomics scheme, characterization of image phenotypes of the tumor, with the potential for decision-making and precision medicine in radiation therapy by predicting treatment outcomes for individual patients rather than one-size-fits-all approach.

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Conflict of interest

The author has no conflict of interest.

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References

- [1] Halperin E, Brady L, Perez C, Wazer D. Perez and Brady's Principles and Practice of Radiation Oncology. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2008. 2106 p
- [2] El Naqa I, Li R, Murphy M. Machine Learning in Radiation Oncology: Theory and Applications. Cham: Springer; 2015. 336 p. DOI: 10.1007/978-3-319-18305-3
- [3] Kansagra AP, Yu JP, Chatterjee AR, Lenchik L, Chow DS, Prater AB, et al. Big data and the future of radiology informatics. *Academic Radiology*. 2016;**23**(1):30-42. DOI: 10.1016/j.acra.2015.10.004
- [4] Lustberg T, van Soest J, Jochems A, Deist T, van Wijk Y, Walsh S, et al. Big data in radiation therapy: Challenges and opportunities. *The British Journal of Radiology*. 2017;**90**(1069):20160689. DOI: 10.1259/bjr.20160689
- [5] Oberije C, Nalbantov G, Dekker A, Boersma L, Borger J, Reymen B, et al. A prospective study comparing the predictions of doctors versus models for treatment outcome of lung cancer patients: A step towards individualized care and shared decision making. *Radiotherapy and Oncology*. 2014;**112**:37-43. DOI: 10.1016/j.radonc.2014.04.012
- [6] El Naqa I, Ruan D, Valdes G, Dekker A, McNutt T, Ge Y, et al. Machine learning and modeling: Data, validation, communication challenges. *Medical Physics*. 2018;**45**(10):e834-e840. DOI: 10.1002/mp.12811
- [7] Mayo CS, Kessler ML, Eisbruch A, Weyburne G, Feng M, Hayman JA, et al. The big data effort in radiation oncology: Data mining or data farming? *Advances in Radiation Oncology*. 2016;**1**(4):260-271. DOI: 10.1016/j.adro.2016.10.001
- [8] Chen RC, Gabriel PE, Kavanagh BD, McNutt TR. How will big data impact clinical decision making and precision medicine in radiation therapy? *International Journal of Radiation Oncology, Biology, Physics*. 2016;**95**(3):880-884. DOI: 10.1016/j.ijrobp.2015.10.052
- [9] Benedict SH, Hoffman K, Martel MK, Abernethy AP, Asher AL, Capala J, et al. Overview of the American Society for Radiation Oncology-National Institutes of Health-American Association of Physicists in Medicine Workshop 2015: Exploring opportunities for radiation oncology in the era of big data. *International Journal of Radiation Oncology, Biology, Physics*. 2016;**95**:873-879. DOI: 10.1016/j.ijrobp.2016.03.006
- [10] ACR Data Science Institute™ to Guide Artificial Intelligence Use in Medical Imaging. 2017. Available at: <https://www.acrdsi.org/-/media/DSI/Files/Strategic-Plan.pdf?la=en>
- [11] Alpaydin E. Introduction to Machine Learning. 3rd ed. Cambridge, MA: The MIT Press; 2014
- [12] Ao S-I, Rieger BB, Amouzegar MA. Machine Learning and Systems Engineering. Dordrecht, NY: Springer; 2010
- [13] Friedman J, Hastie T, Tibshirani R. The Elements of Statistical Learning. Vol. 1. Berlin: Springer; 2001
- [14] Feng M, Valdes G, Dixit N, Solberg TD. Machine learning in radiation oncology: Opportunities, requirements, and needs. *Frontiers in Oncology*. 2018;**8**:110. DOI: 10.3389/fonc.2018.00110
- [15] Suzuki K, Armato SG 3rd, Li F, Sone S, Doi K. Massive training artificial neural network (MTANN) for reduction

- of false positives in computerized detection of lung nodules in low-dose computed tomography. *Medical Physics*. 2003;**30**(7):1602-1617. DOI: 10.1118/1.1580485
- [16] Chan HP, Lo SC, Sahiner B, Lam KL, Helvie MA. Computer-aided detection of mammographic microcalcifications: Pattern recognition with an artificial neural network. *Medical Physics*. 1995;**22**(10):1555-1567. DOI: 10.1118/1.597428
- [17] Zhu Y, Wang L, Liu M, Qian C, Yousuf A, Oto A, et al. MRI-based prostate cancer detection with high-level representation and hierarchical classification. *Medical Physics*. 2017;**44**(3):1028-1039. DOI: 10.1002/mp.12116
- [18] Rezaei M, Yang H, Meinel C. Deep neural network with l2-norm unit for brain lesions detection. In: Liu D, Xie S, Li Y, Zhao D, El-Alfy ES, editors. *Neural Information Processing. ICONIP 2017*. Cham: Springer; 2017. pp. 798-807. DOI: 10.1007/978-3-319-70093-9_85
- [19] Cheng JZ, Ni D, Chou YH, Qin J, Tiu CM, Chang YC, et al. Computer-aided diagnosis with deep learning architecture: Applications to breast lesions in US images and pulmonary nodules in CT scans. *Scientific Reports*. 2016;**6**:24454. DOI: 10.1038/srep24454
- [20] Feng PH, Lin Y, Lo GM. A machine learning texture model for classifying lung cancer subtypes using preliminary bronchoscopic findings. *Medical Physics*. 2018;**45**(12):5509-5514. DOI: 10.1002/mp.13241
- [21] Beig N, Khorrami M, Alilou M, et al. Perinodular and intranodular radiomic features on lung CT images distinguish adenocarcinomas from granulomas. *Radiology*. 2018;**290**(3):1-10. <https://doi.org/10.1148/radiol.2018180910>
- [22] Joo S, Yang YS, Moon WK, Kim HC. Computer-aided diagnosis of solid breast nodules: Use of an artificial neural network based on multiple sonographic features. *IEEE Transactions on Medical Imaging*. 2004;**23**(10):1292-1300. DOI: 10.1109/TMI.2004.834617
- [23] Valdes G, Luna JM, Eaton E, Simone CB II, Ungar LH, Solberg TD. MediBoost: A patient stratification tool for interpretable decision making in the era of precision medicine. *Scientific Reports*. 2016;**6**:37854. DOI: 10.1038/srep37854
- [24] Caruana R, Lou Y, Gehrke J, Koch P, Sturm M, Elhadad N. Intelligible models for healthcare: Predicting pneumonia risk and hospital 30-day readmission. In: *Proceedings of the 21th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*. New York, USA: ACM; 2015. pp. 1721-1730. DOI: 10.1145/2783258.2788613
- [25] Caruana R, Niculescu-Mizil A. An empirical comparison of supervised learning algorithms. In: *Proceedings of the 23rd International Conference on Machine Learning*. Pittsburgh: ACM; 2006. pp. 161-168. DOI: 10.1145/1143844.1143865
- [26] Fernández-Delgado M, Cernadas E, Barro S, Amorin D. Do we need hundreds of classifiers to solve real world classification problems. *Journal of Machine Learning Research*. 2014;**15**:3133-3181
- [27] Fayad H, Gilles M, Pan T, Visvikis D. A 4D global respiratory motion model of the thorax based on CT images: A proof of concept. *Medical Physics*. 2018;**45**(7):3043-3051. DOI: 10.1002/mp.12982
- [28] Steiner E, Shieh C, Caillet V, O'Brien R, et al. WE-HI-KDBRB1-10: 4DCT and 4DCBCT under-predict intrafraction lung target motion during radiotherapy. *Medical Physics*. 2018;**45**(6):e646-e647. DOI: 10.1002/mp.12938

- [29] Dick D, Wu X, Zhao W. MO-E115-GePD-F5-3: Fiducial-less tracking for the radiation therapy of liver tumors using artificial neural networks. *Medical Physics*. 2018;**45**(6):e415-e415. DOI: 10.1002/mp.12938
- [30] Johansson A, Balter J, Cao Y. WE-AB-202-5: Gastrointestinal 4D MRI with respiratory motion correction. *Medical Physics*. 2018;**45**(6):e583-e583. DOI: 10.1002/mp.12938
- [31] Nie D, Cao X, Gao Y, Wang L, Shen D. Estimating CT image from MRI data using 3D fully convolutional networks. In: Carneiro G et al., editors. *Deep Learning and Data Labeling for Medical Applications. DLMIA 2016, LABELS 2016. LNCS. Vol. 10008*. Cham: Springer; 2016. pp. 170-178. DOI: 10.1007/978-3-319-46976-8_18
- [32] Bayisa F, Liu X, Garpebring A, Yu J. Statistical learning in computed tomography image estimation. *Medical Physics*. 2018;**45**(12):5450-5460. DOI: 10.1002/mp.13204
- [33] Huynh T, Gao Y, Kang J, et al. Estimating CT image from MRI data using structured random forest and auto-context model. *IEEE Transactions on Medical Imaging*. 2016;**35**(1):174-183. DOI: 10.1109/TMI.2015.2461533
- [34] Chen S, Qin A, Zhou D, Yan D. Technical note: U-net-generated synthetic CT images for magnetic resonance imaging-only prostate intensity-modulated radiation therapy treatment planning. *Medical Physics*. 2018;**45**(12):5659-5665. DOI: 10.1002/mp.13247
- [35] Bahrami K, Shi F, Rekik I, Shen D. Convolutional neural network for reconstruction of 7T-like images from 3T MRI using appearance and anatomical features. In: Carneiro G et al., editors. *Deep Learning and Data Labeling for Medical Applications*. Cham, Switzerland: Springer, Verlag; 2016. pp. 39-47. DOI: 10.1007/978-3-319-46976-8_5
- [36] Bahrami K, Shi F, Zong X, Shin HW, An H, Shen D. Reconstruction of 7T-like images from 3T MRI. *IEEE Transactions on Medical Imaging*. 2016;**35**(9):2085-2097. DOI: 10.1109/TMI.2016.2549918
- [37] Bahrami K, Rekik I, Shi F, Gao Y, Shen D. 7T-guided learning framework for improving the segmentation of 3T MR images. *Medical Image Computing and Computer-Assisted Intervention*. 2016;**9901**:572-580. DOI: 10.1007/978-3-319-46723-8_66
- [38] Bahrami K, Shi F, Rekik I, Gao Y, Shen D. 7T-guided super-resolution of 3T MRI. *Medical Physics*. 2017;**44**(5):1661-1677. DOI: 10.1002/mp.12132
- [39] Guerrero T, Zhang G, Huang TC, Lin KP. Intrathoracic tumour motion estimation from CT imaging using the 3D optical flow method. *Physics in Medicine and Biology*. 2004;**49**(17):4147-4161
- [40] Zhang T, Chi Y, Meldolesi E, Yan D. Automatic delineation of on-line head-and-neck computed tomography images: Toward on-line adaptive radiotherapy. *International Journal of Radiation Oncology, Biology, Physics*. 2007;**68**(2):522-530. DOI: 10.1016/j.ijrobp.2007.01.038
- [41] Hu S, Wei L, Gao Y, Guo Y, Wu G, Shen D. Learning-based deformable image registration for infant MR images in the first year of life. *Medical Physics*. 2017;**44**(1):158-170. DOI: 10.1002/mp.12007
- [42] Zagoruyko S, Komodakis N. Learning to compare image patches via convolutional neural networks. *IEEE Conference on Computer Vision and Pattern Recognition*. 2015:4353-4361. DOI: 10.1109/CVPR.2015.7299064

- [43] Jiang D, Shi Y, Chen X, Wang M, Song Z. Fast and robust multimodal image registration using a local derivative pattern. *Medical Physics*. 2017;**44**(2):497-509. DOI: 10.1002/mp.12049
- [44] Neylon J, Min Y, Low DA, Santhanam A. A neural network approach for fast, automated quantification of DIR performance. *Medical Physics*. 2017;**44**(8):4126-4138. DOI: 10.1002/mp.12321
- [45] Wu J, Su Z, Li Z. A neural network-based 2D/3D image registration quality evaluator for pediatric patient setup in external beam radiotherapy. *Journal of Applied Clinical Medical Physics*. 2016;**17**(1):22-33. DOI: 10.1120/jacmp.v17i1.5235
- [46] Wu G, Kim M, Wang Q, Munsell BC, Shen D. Scalable high-performance image registration framework by unsupervised deep feature representations learning. *IEEE Transactions on Biomedical Engineering*. 2016;**63**(7):1505-1516. DOI: 10.1109/TBME.2015.2496253
- [47] Kearney V, Haaf S, Sudhyadhom A, Valdes G, Solberg TD. An unsupervised convolutional neural network-based algorithm for deformable image registration. *Physics in Medicine and Biology*. 2018;**63**(18):185017. DOI: 10.1088/1361-6560/aada66
- [48] International Commission of Radiation Units and Measurements. *The ICRU Report 83: Prescribing, Recording and Reporting Photon-beam Intensity Modulated Radiation Therapy (IMRT)*. Oxford University Press; 2010. 107 p. DOI: 10.1093/jicru/ndq002
- [49] Podgorsak EB. *Radiation Oncology Physics: A Handbook for Teachers and Students*. International Atomic Energy Agency (IAEA): IAEA; 2005. 657 p
- [50] Menze BH, Jakab A, Bauer S, Kalpathy-Cramer J, Farahani K, et al. The multimodal brain tumor image segmentation benchmark (BRATS). *IEEE Transactions on Medical Imaging*. 2015;**34**(10):1993-2024. DOI: 10.1109/TMI.2014.2377694
- [51] Bakas S, Akbari H, Sotiras A, Bilello M, Rozycki M, Kirby J, et al. Segmentation Labels and radiomic features for the pre-operative scans of the TCGA-GBM collection. *The Cancer Imaging Archive*. 2017. DOI: 10.7937/K9/TCIA.2017.KLXWJJ1Q
- [52] Osman AFI. Automated brain tumor segmentation on magnetic resonance images and patient's overall survival prediction using support vector machines. In: Crimi A, Bakas S, Kuijf H, Menze B, Reyes M, editors. *Brainlesion: Glioma, Multiple Sclerosis, Stroke and Traumatic Brain Injuries*. Cham: Springer; 2018. pp. 435-449. DOI: 10.1007/978-3-319-75238-9_37
- [53] Kamnitsas K, Bai W, Ferrante E, et al. Ensembles of multiple models and architectures for robust brain tumour segmentation. In: Crimi A, Bakas S, Kuijf H, Menze B, Reyes M, editors. *Brain Les 2017*. LNCS. Vol. 10670. Cham: Springer; 2018. pp. 450-462. DOI: 10.1007/978-3-319-75238-9_38
- [54] Kamnitsas K, Ledig C, Newcombe VF, et al. Efficient multi-scale 3D CNN with fully connected CRF for accurate brain lesion segmentation. *Medical Image Analysis*. 2017;**36**:61-78. DOI: 10.1016/j.media.2016.10.004
- [55] Pereira S, Pinto A, Alves V, Silva CA. Brain tumor segmentation using convolutional neural networks in MRI images. *IEEE Transactions on Medical Imaging*. 2016;**35**(5):1240-1251. DOI: 10.1109/TMI.2016.2538465
- [56] Guo Y, Gao Y, Shen D. Deformable MR prostate segmentation via deep feature learning and sparse patch matching. *IEEE Transactions on Medical*

Imaging. 2016;**35**(4):1077-1089. DOI: 10.1109/TMI.2015.2508280

[57] Men K, Dai J, Li Y. Automatic segmentation of the clinical target volume and organs at risk in the planning CT for rectal cancer using deep dilated convolutional neural networks. *Medical Physics*. 2017;**44**(12): 6377-6389. DOI: 10.1002/mp.12602

[58] Carass A, Roy S, Jog A, Cuzzocreo JL, Magrath E, Gherman A, et al. Longitudinal multiple sclerosis lesion segmentation: Resource and challenge. *NeuroImage*. 2017;**148**:77-102. DOI: 10.1016/j.neuroimage.2016.12.064

[59] Yang X, Wu N, Cheng G, Zhou Z, Yu DS, Beitler JJ, et al. Automated segmentation of the parotid gland based on atlas registration and machine learning: A longitudinal MRI study in head-and-neck radiation therapy. *International Journal of Radiation Oncology, Biology, Physics*. 2014;**90**(5):1225-1233. DOI: 10.1016/j.ijrobp.2014.08.350

[60] Ibragimov B, Xing L. Segmentation of organs-at-risks in head and neck CT images using convolutional neural networks. *Medical Physics*. 2017;**44**(2):547-557. DOI: 10.1002/mp.12045

[61] LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature*. 2015;**521**(7553): 436-444. DOI: 10.1038/nature14539

[62] Thompson RF, Valdes G, Fuller CD, Carpenter CM, Morin O, Aneja S, et al. Artificial intelligence in radiation oncology: A specialty-wide disruptive transformation? *Radiotherapy and Oncology*. 2018;**129**(3):421-426. DOI: 10.1016/j.radonc.2018.05.030

[63] Nwankwo O, Mekdash H, Sihono DS, Wenz F, Glatting G. Knowledge-based radiation therapy (KBRT) treatment planning versus planning by experts: Validation of a KBRT algorithm

for prostate cancer treatment planning. *Radiation Oncology*. 2015;**10**:111. DOI: 10.1186/s13014-015-0416-6

[64] Li N, Carmona R, Sirak I, Kasaova L, Followill D, Michalski J, et al. Highly efficient training, refinement, and validation of a knowledge-based planning quality-control system for radiation therapy clinical trials. *International Journal of Radiation Oncology, Biology, Physics*. 2017;**97**(1):164-172. DOI: 10.1016/j.ijrobp.2016.10.005

[65] Chatterjee A, Serban M, Abdulkarim B, Panet-Raymond V, Souhami L, Shenouda G, et al. Performance of knowledge-based radiation therapy planning for the glioblastoma disease site. *International Journal of Radiation Oncology, Biology, Physics*. 2017;**99**(4):1021-1028. DOI: 10.1016/j.ijrobp.2017.07.012

[66] Tol JP, Delaney AR, Dahele M, Slotman BJ, Verbakel WF. Evaluation of a knowledge-based planning solution for head and neck cancer. *International Journal of Radiation Oncology, Biology, Physics*. 2015;**91**(3):612-620. DOI: 10.1016/j.ijrobp.2014.11.014

[67] Foy JJ, Marsh R, Ten Haken RK, Younge KC, Schipper M, Sun Y, et al. An analysis of knowledge-based planning for stereotactic body radiation therapy of the spine. *Practical Radiation Oncology*. 2017;**7**(5):e355-e360. DOI: 10.1016/j.prro.2017.02.007

[68] Valdes G, Simone CB, Chen J, Lin A, Yom SS, et al. Clinical decision support of radiotherapy treatment planning: A data-driven machine learning strategy for patient-specific dosimetric decision making. *Radiotherapy and Oncology*. 2017;**125**(3):392-397. DOI: 10.1016/j.radonc.2017.10.014

[69] Zhu X, Ge Y, Li T, Thongphiew D, Yin FF, Wu QJ. A planning quality evaluation tool for prostate adaptive IMRT based on machine learning.

Medical Physics. 2011;**38**(2):719-726. DOI: 10.1118/1.3539749

[70] Moore KL, Schmidt R, Moiseenko V, Olsen LA, Tan J, Xiao Y, et al. Quantifying unnecessary normal tissue complication risks due to suboptimal planning: A secondary study of RTOG 0126. *International Journal of Radiation Oncology, Biology, Physics*. 2015;**92**(2):228-235. DOI: 10.1016/j.ijrobp.2015.01.046

[71] Rowbottom CG, Webb S, Oldham M. Beam-orientation customization using an artificial neural network. *Physics in Medicine and Biology*. 1999;**44**:2251. DOI: 10.1088/0031-9155/44/9/312

[72] Llacer J, Li S, Agazaryan N, Promberger C, Solberg TD. Non-coplanar automatic beam orientation selection in cranial IMRT: A practical methodology. *Physics in Medicine and Biology*. 2009;**54**(5):1337-1368. DOI: 10.1088/0031-9155/54/5/016

[73] Silver D, Huang A, Maddison CJ, Guez A, Sifre L, van den Driessche G, et al. Mastering the game of go with deep neural networks and tree search. *Nature*. 2016;**529**:484-489. DOI: 10.1038/nature16961

[74] Li Q, Chan MF. Predictive time-series modeling using artificial neural networks for Linac beam symmetry: An empirical study. *Annals of the New York Academy of Sciences*. 2017;**1387**(1): 84-94. DOI: 10.1111/nyas.13215

[75] El Naqa I. SU-E-J-69: An anomaly detector for radiotherapy quality assurance using machine learning. *Medical Physics*. 2011;**38**:3458. DOI: 10.1118/1.3611837

[76] Ford EC, Terezakis S, Souranis A, Harris K, Gay H, Mutic S. Quality control quantification (QCQ): A tool to measure the value of quality control checks in radiation

oncology. *International Journal of Radiation Oncology, Biology, Physics*. 2012;**84**(3):e263-e269. DOI: 10.1016/j.ijrobp.2012.04.036

[77] Hoisak JD, Pawlicki T, Kim GY, Fletcher R, Moore KL. Improving linear accelerator service response with a real-time electronic event reporting system. *Journal of Applied Clinical Medical Physics*. 2014;**15**(5):4807. DOI: 10.1120/jacmp.v15i5.4807

[78] Huq MS, Fraass BA, Dunscombe PB, Gibbons JP Jr, Ibbott GS, et al. The report of task group 100 of the AAPM: Application of risk analysis methods to radiation therapy quality management. *Medical Physics*. 2016;**43**(7):4209. DOI: 10.1118/1.4947547

[79] Osman A, Maalej N, Jayesh K. SU-K-KDBRA1-01: A novel learning approach for predicting MLC positioning during dynamic IMRT delivery. *Medical Physics*. 2018;**45**(6):e357-e358. DOI: 10.1002/mp.12938

[80] Valdes G, Morin O, Valenciaga Y, Kirby N, Pouliot J, Chuang C. Use of TrueBeam developer mode for imaging QA. *Journal of Applied Clinical Medical Physics*. 2015;**16**(4):322-333. DOI: 10.1120/jacmp.v16i4.5363

[81] Valdes G, Scheuermann R, Hung CY, Olszanski A, Bellerive M, Solberg TD. A mathematical framework for virtual IMRT QA using machine learning. *Medical Physics*. 2016;**43**(7):4323. DOI: 10.1118/1.4953835

[82] Valdes G, Chan MF, Lim SB, Scheuermann R, Deasy JO, Solberg TD. IMRT QA using machine learning: A multi-institutional validation. *Journal of Applied Clinical Medical Physics*. 2017;**18**(5):279-284. DOI: 10.1002/acm2.12161

[83] Carlson JN, Park JM, Park SY, Park JI, Choi Y, Ye SJ. A machine learning

approach to the accurate prediction of multi-leaf collimator positional errors. *Physics in Medicine and Biology*. 2016;**61**(6):2514-2531. DOI: 10.1088/0031-9155/61/6/2514

[84] Liu C, Kim J, Kumarasiri A, Mayyasa E, Browna S, Wen N, et al. An automated dose tracking system for adaptive radiation therapy. *Computer Methods and Programs in Biomedicine*. 2018;**154**:1-8. DOI: 10.1016/j.cmpb.2017.11.001

[85] Guidi G, Maffei N, Meduri B, D'Angelo E, Mistretta GM, et al. A machine learning tool for re-planning and adaptive RT: A multicenter cohort investigation. *Physica Medica*. 2016;**32**(12):1659-1666. DOI: 10.1016/j.ejmp.2016.10.005

[86] Chetvertkov MA, Siddiqui F, Kim J, Chetty I, Kumarasiri A, Liu C, et al. Use of regularized principal component analysis to model anatomical changes during head and neck radiation therapy for treatment adaptation and response assessment. *Medical Physics*. 2016;**43**(10):5307-5319. DOI: 10.1118/1.4961746

[87] Tseng HH, Luo Y, Cui S, Chien JT, Ten Haken RK, Naqa IE. Deep reinforcement learning for automated radiation adaptation in lung cancer. *Medical Physics*. 2017;**44**:6690-6705. DOI: 10.1002/mp.12625

[88] Varfalvy N, Piron O, Cyr MF, Dagnault A, Archambault L. Classification of changes occurring in lung patient during radiotherapy using relative γ analysis and hidden Markov models. *Medical Physics*. 2017;**44**:5043-5050. DOI: 10.1002/mp.12488

[89] Lee S, Ybarra N, Jeyaseelan K, Faria S, Kopek N, Brisebois P, et al. Bayesian network ensemble as a multivariate strategy to predict radiation pneumonitis risk. *Medical Physics*. 2015;**42**(5):2421-2430. DOI: 10.1118/1.4915284

[90] Naqa IE, Deasy JO, Mu Y, Huang E, Hope AJ, Lindsay PE, et al. Datamining approaches for modeling tumor control probability. *Acta Oncologica*. 2010;**49**(8):1363-1373. DOI: 10.3109/02841861003649224

[91] Zhen X, Chen J, Zhong Z, Hrycushko B, Zhou L, Jiang S, et al. Deep convolutional neural network with transfer learning for rectum toxicity prediction in cervical cancer radiotherapy: A feasibility study. *Physics in Medicine and Biology*. 2017;**62**(21):8246-8263. DOI: 10.1088/1361-6560/aa8d09

[92] Deist TM, Dankers FJWM, Valdes G, Wijsman R, Hsu IC, Oberije C, et al. Machine learning algorithms for outcome prediction in (chemo)radiotherapy: An empirical comparison of classifiers. *Medical Physics*. 2018;**45**(7):3449-3459. DOI: 10.1002/mp.12967

[93] Yahya N, Ebert MA, Bulsara M, House MJ, Kennedy A, Joseph DJ, et al. Statistical-learning strategies generate only modestly performing predictive models for urinary symptoms following external beam radiotherapy of the prostate: A comparison of conventional and machine-learning methods. *Medical Physics*. 2016;**43**(5):2040. DOI: 10.1118/1.4944738

[94] Zhang HH, D'Souza WD, Shi L, Meyer RR. Modeling plan-related clinical complications using machine learning tools in a multiplan IMRT framework. *International Journal of Radiation Oncology, Biology, Physics*. 2009;**74**(5):1617-1626. DOI: 10.1016/j.ijrobp.2009.02.065

[95] Kang J, Schwartz R, Flickinger J, Beriwal S. Machine learning approaches for predicting radiation therapy outcomes: A Clinician's perspective. *International Journal of Radiation Oncology, Biology, Physics*. 2015;**93**(5):1127-1135. DOI: 10.1016/j.ijrobp.2015.07.2286

- [96] Baumann M, Krause M, Overgaard J, Debus J, Bentzen SM, Daartz J, et al. Radiation oncology in the era of precision medicine. *Nature Reviews. Cancer*. 2016;**16**(4):234-249. DOI: 10.1038/nrc.2016.18
- [97] Arimura H, Soufi M, Kamezawa H, Ninomiya K, Yamada M. Radiomics with artificial intelligence for precision medicine in radiation therapy. *Journal of Radiation Research*. 2018;**60**(1):150-157. DOI: 10.1093/jrr/rry077
- [98] Aerts HJ, Velazquez ER, Leijenaar RT, Parmar C, Grossmann P, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. *Nature Communications*. 2014;**5**:4006. DOI: 10.1038/ncomms5006
- [99] Depeursinge A, Yanagawa M, Leung AN, Rubin DL. Predicting adenocarcinoma recurrence using computational texture models of nodule components in lung CT. *Medical Physics*. 2015;**42**(4):2054-2063. DOI: 10.1118/1.4916088
- [100] Lambin P, Rios-Velazquez E, Leijenaar R, Carvalho S, van Stiphout RG, Granton P, et al. Radiomics: Extracting more information from medical images using advanced feature analysis. *European Journal of Cancer*. 2012;**48**(4):441-446. DOI: 10.1016/j.ejca.2011.11.036
- [101] Wu J, Tha KK, Xing L, Li R. Radiomics and radiogenomics for precision radiotherapy. *Journal of Radiation Research*. 2018;**59**(suppl_1): i25-i31. DOI: 10.1093/jrr/rrx102
- [102] Lao J, Chen Y, Li ZC, Li Q, Zhang J, Liu J, et al. A deep learning-based radiomics model for prediction of survival in glioblastoma multiforme. *Scientific Reports*. 2017;**7**:10353. DOI: 10.1038/s41598-017-10649-8
- [103] Gulshan V, Peng L, Coram M, Stumpe MC, Wu D, Narayanaswamy A, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. *The Journal of the American Medical Association*. 2016;**316**:2402-2410. DOI: 10.1001/jama.2016.17216
- [104] Mayo CS, Moran JM, Bosch W, Xiao Y, McNutt T, Popple R, et al. American Association of Physicists in Medicine Task Group 263: Standardizing nomenclatures in radiation oncology. *International Journal of Radiation Oncology, Biology, Physics*. 2018;**100**(4):1057-1066. DOI: 10.1016/j.ijrobp.2017.12.013
- [105] Luo W, Phung D, Tran T, et al. Guidelines for developing and reporting machine learning predictive models in biomedical research: A multidisciplinary view. *Journal of Medical Internet Research*. 2016;**18**(12):e323. DOI: 10.2196/jmir.5870
- [106] Parodi S, Riccardi G, Castagnino N, Tortolina L, Maffei M, Zoppoli G, et al. Systems medicine in oncology: Signaling network modeling and new generation decision-support systems. *Methods in Molecular Biology*. 2016;**1386**:181-219. DOI: 10.1007/978-1-4939-3283-2_10
- [107] Memorial Sloan Kettering Cancer Center. Watson oncology. n.d. <https://www.mskcc.org/about/innovative-collaborations/watson-oncology> [Accessed: 30 January 2019]
- [108] Kohn MS, Sun J, Knoop S, Shabo A, Carmeli B, Sow D, et al. IBM's health analytics and clinical decision support. *Yearbook of Medical Informatics*. 2014;**9**:154-162. DOI: 10.15265/IY-2014-0002
- [109] Bibault JE, Giraud P, Burgun A. Big data and machine learning in radiation oncology: State of the art and future prospects. *Cancer Letters*. 2016;**382**(1):110-117. DOI: 10.1016/j.canlet.2016.05.033