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Use of Big Data for Quality Assurance in Radiation Therapy

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The application of big data to the quality assurance of radiation therapy is multifaceted. Big data can be used to detect anomalies and suboptimal quality metrics through both statistical means and more advanced machine learning and artificial intelligence. The application of these methods to clinical practice is discussed through examples of guideline adherence, contour integrity, treatment delivery mechanics, and treatment plan quality. The ultimate goal is to apply big data methods to direct measures of patient outcomes for care quality. The era of big data and machine learning is maturing and the implementation for quality assurance promises to improve the quality of care for patients.
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Introduction

Quality assurance, the systematic monitoring and evaluation of safety and quality metrics, is multifaceted through the complex, multistep process required to deliver radiation therapy safely to all patients. There are up to 269 defined steps in the process of safely treating patients with radiation,[1] and each step is hypothetically prone to an error that could result in downstream negative impact to the patient. Considerable effort is made at each phase of the treatment process to provide redundant checks, secondary independent measurements, and evaluations against practice standards. "Big data" offer opportunities to provide more thorough evaluations at key steps in the process, and to both automate and personalize the quality assurance methods resulting in more efficient, safer, and higher quality care to each individual patient.

Big data store the experience from the past and allow extrapolation to current patients to detect anomalies and potential errors. In the simplest form, if a new patient follows the process and treatment plans of similar patients treated in the past that resulted in safe and efficacious treatment, then the new patient's treatment also should remain safe and effective. Big data seek to evaluate how this new patient's care plan fits into a range of past patients and treatments—Is it within the norms, or is it anomalous in some way that could pose a risk? The key is in recalling the relevant past experience from the data that align with the new patient. We need to define what characterizes this new patient, such that we can identify similar patients from the past to compare it with, and also to define what measures we can evaluate to assess the new patient's treatment in comparison to past treatments. In short, the goal is to identify a cohort of similar patients from the past and evaluate treatment related features in the new patient that may be anomalies. The potential for clinically relevant improvements utilizing big data are vast, and will be explored in this manuscript.

At the same time, big data offer unparalleled opportunities for improving quality of care. As this field evolves, it will also be important not to over-rely on it, as existing knowledge is sometimes suppressed (or controlled for) in practice. For example, if every past patient has received a dose to an organ that is lower than a specific threshold, there is no knowledge in the data of how a higher dose would impact patients; without attention to this, prediction models may not recognize the importance of keeping the dose lower than the threshold and in the range of prior cases. Also, some data may become obsolete as clinical practice improves and evolves beyond earlier approaches or technologies. We generally do not want to treat patients like we did 20-30 years ago, meaning the pool of relevant data must continually evolve with practice changes and delivery improvements. Understanding the specific application of big data to quality assurance and how it interrelates with current quality assurance practices is key to advancing our practice to realize the full potential it may bring. The challenge will be to identify optimal measures and apply them appropriately to new patients.

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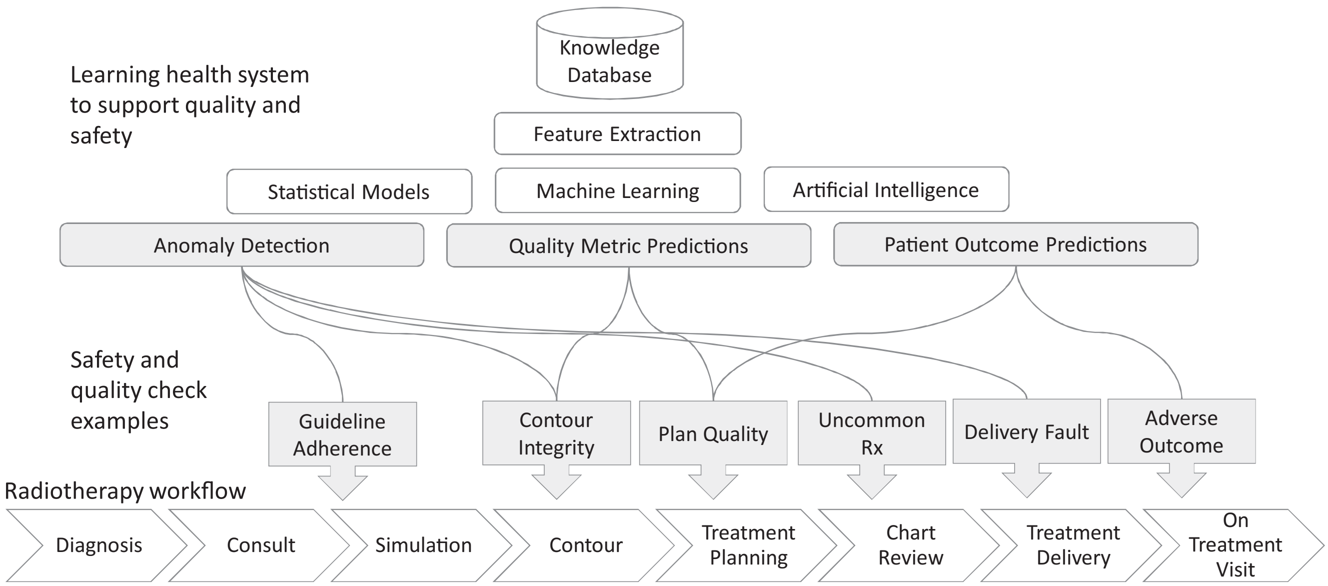


Figure 1 A big data learning health system providing electronic oversight to the quality and safety in the workflow of radiation therapy. Such a system can support the creation of anomaly detection, quality predictions and patient outcome predictions using advance statistical methods, machine learning and artificial intelligence to support the electronic detection of poor quality or safety risks using data acquired during the workflow.

Figure 1 displays a potential framework for including various data driven quality and safety checks into the clinical workflow. The examples described in the manuscript are identified to help understand how the quality models may fit into the existing radiation oncology clinical environment.

How Can Big Data Impact Quality?

A basic premise of quality is to do things the same way every time, which is straightforward and well documented in manufacturing processes.[2] Another basic premise is to measure anything that you would like to improve upon. Finally, the evaluation of those measures can provide insight into how quality can be improved. Often times these measurements provide real-time feedback to the manufacturing process, important to prevent errors.

When applying these manufacturing principles to clinical care, there is one key complication, which is that each patient is different. In the clinical setting, it is desirable to do some process steps the same way every time, but it is also necessary to tailor treatments to unique patient cases and variable patient anatomy. This is where big data come in, allowing us to store a large range of patients that we have treated in the past enabling access to similar patients, thus providing a cohort that we should be treating in a very similar way. The more data we have, the more refined we can be with the cohort. This allows big data to move away from population-based metrics for quality and allows the metrics to be specific to each cohort and learned from the past experience.

If we wanted to look at treatment delivery complexity, such as the complexity of the leaf sequencing for intensity modulated radiotherapy (IMRT), then a feature used to identify a similar cohort may represent the complexity of the target shape such as a surface area to volume ratio, or level of concavity. Identifying the most relevant features that impact the quality metric allows us to refine the cohort, and best determine the appropriate limits on the quality metric for that specific group.

As we explore different methods of data science used for quality assurance, the goal is to characterize the patient and attributes of their care to determine or predict an expected quality metric for that patient. Then the assessment of that quality metric is the comparison between the actual achieved outcome against the predicted outcome, and ensure that any differences are within an acceptable range.

Methods to Detect Errors and Quality Differences

Quality assurance is a broad area for big data and can take the form of error prevention through detection of anomalies or uncommon scenarios that may be prone to error. Detection of "poor quality" can be somewhat subjective and is typically represented by a comparison to a patient specific prediction of quality metrics to judge if the patient is receiving the highest quality of care.

Methods to detect errors based on prior data fall into a few different categories. The simplest form is perhaps a statistical outlier test where an assessment is performed for the new patient and is compared with the cohort of similar patients and evaluated to see if it is an outlier. A simple example may be bladder volume for prostate patients who are treated with a full bladder. A patient whose bladder is unintentionally empty at the time of simulation may have smaller volume that is a statistical outlier from a cohort of similar prostate patients who were simulated with a full bladder. Statistical outlier tests may be from standard deviation or interquartile range evaluations, and the metrics used can be any numeric assessment that can be calculated based on the new patient data and a similar cohort with enough samples to obtain statistical significance. These methods are highly dependent on proper cohort selection.

A second set of methods are directly derived algorithms that include knowledge of the system and are derived specifically for a given task, but use prior data for comparison. Examples of this include knowledge-based treatment planning for achievable dose volume histograms or methods that know an underlying workflow and identify anomalies in that workflow that might deviate from the normal variations seen in prior patients. This type of method looks at the probabilities of a sequence of events being carried out in a particular way, and identifies anomalies in that sequence.

The algorithms get more complex as we add dependent variables. As we explore more features of the patients, we enter machine learning models that can be trained. With these models, such as classification and regression trees or random forest, we can build models to predict a particular measure. We can then use that model to predict an expectation for a particular patient, and if the metric does not meet that expectation, it can be viewed as an anomaly.

With artificial intelligence models such as convolution neural networks, data can be used to train models with both high quality data and data known to have errors. In these models, there is no longer a formal statistics methodology, but rather a neural network that is trained by repeatedly sending it feature vectors with a known outcome until the system learns to identify the outcome correctly when presented with the same features of a new patient. This model is commonly used for object identification in digital photographs. Such methods have become popular in automated image segmentation, and can be adapted toward quality assurance and safety monitoring by training them to detect when something such as a region of interest is incorrect or suboptimal.

Examples of Quality and Safety in Radiotherapy

One of the safety mantras in medicine is to treat the right patient with the right medicine, and right dose, at the right time, for the right reason to get the right result. The same is true in radiation oncology, and big data can help us with some of these "rights."

A straightforward example is using data from prior patients to detect uncommon prescriptions for specific diagnoses, treatment intent (palliative vs definitive) and treatment site. A prescription that is an outlier for a particular patient scenario can alert to a potential error. Sharabi et al[3] proposed a method of cross-referencing of prescriptions with diagnosis and morphology codes to highlight dose and fractionation that were uncommonly used as a component of peer review.[4]

Adherence to guidelines is often cited as a means for maintaining quality of care. However, many guidelines offer choices and individual patient decisions that are within a relatively broad range, or allow for appropriate deviations from the guidelines. For example, the dose range for the treatment of a bone metastasis could range from 16 to 20 Gy in a single fraction using a stereotactic technique, to a longer course of fractionated radiation[5] depending on the clinical scenario. Razavi et al[6] proposes a data driven refinement for the guidelines that derives rules from prior repetitive patterns of non-compliance to assist in assessing the quality of care based on guideline adherence. In their example, a guideline may suggest that postmastectomy radiation can be avoided in selected patients over 75, but that postmastectomy radiation should be considered in patients with tumors over 5 cm. Thus, the decision of whether to treat a 76-year-old patient with a tumor over 5 cm would be a nuanced clinical decision weighing multiple potentially conflicting patient-specific factors, including a lower risk based on age vs a higher risk based on tumor size. In the strict sense, a treatment decision for this patient example may not adhere to a particular guideline, but in a data driven sense, the algorithms can learn that the decision to treat with radiation occurs with some frequency in these cases as it is left up to clinicians and patients when close to guideline thresholds. This type of model serves to fill the gap between clinician's practice learned from the data and guidelines as existing best practices to improve the appropriateness of safety alerts for quality.[7]

Radiation therapy depends on the integrity of contours used to identify both target volumes and normal anatomy to be avoided.[8] Significant efforts have been made on automated image segmentation to improve efficiency. However, from a safety point of view, we can also seek to assess contour integrity through anomaly detection from big data. Shah et al[9] used both direct methods such as contiguousness tests and data-driven methods such as outlier detection based on the extent of regions in single direction to identify region of interest anomalies. McIntosh et al[10] applied a random forest method to classify and evaluate contour integrity to improve safety. Advancements and refinements in our ability to detect subtle anomalies in contouring can help detect currently unrecognized errors in treatment. Furthermore, it may help in broader based assessment of practice differences between clinicians.

Another example in which the big data concept can improve treatment quality is to minimize treatment disruption caused by fatal multileft collimator (MLC) failures, requiring motor or T-Nut replacement for treatment resumption.[11] Wu et al proposes a data-driven method utilizing historical MLC performance data, for example, linear accelerator-generated trajectory logs and documented failures in service reports, to predict MLC malfunctions for preventive maintenance. Specifically, a digital counter concept is introduced for quantifying MLC performance from trajectory logs by way of counting leaf/carriage deviation events.

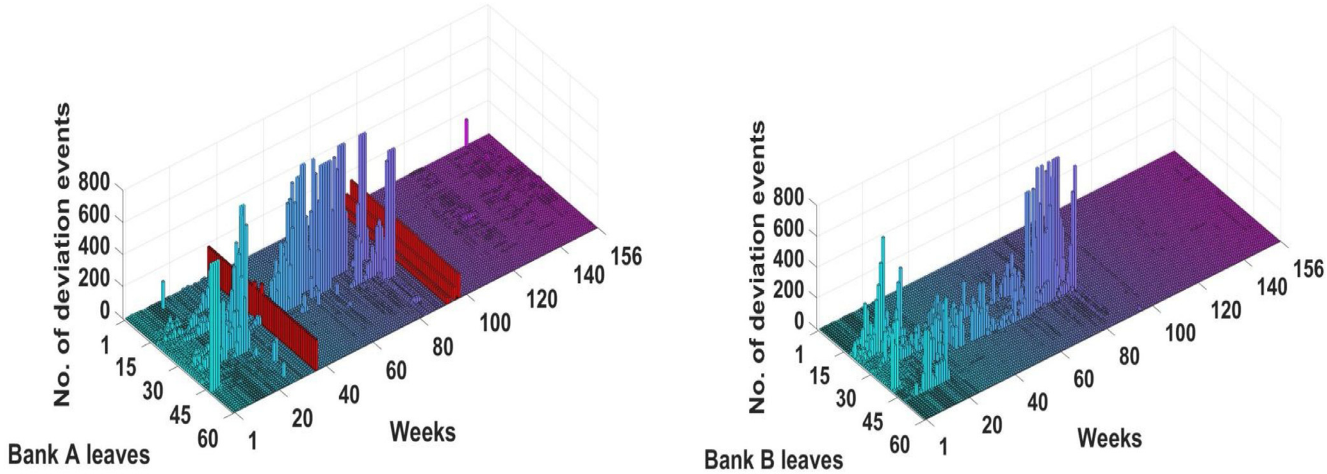


Figure 2 Distributions of a Varian TrueBeam's deviation events calculated from 35,851 trajectory logs. X-axis represents the leaf number from 1 to 60; y-axis represents logs' creation time sorted in weeks: 156 weeks from January 5, 2015 to December 29, 2017; z-axis represents the number of deviation events per week. The deviation distributions are then associated with documented failures to find a predictive model for minimizing treatment disruption.

The distributions of deviation events as shown in Figure 2 are then associated with the documented failures to establish a predictive model for preventive maintenance. In a retrospective demonstration on a Truebeam (Varian, Palo Alto, CA)'s 3-year failure data, the model if implemented in clinic could predict 16 hardware failures, offering a pathway to experiment preventive maintenance that reduce treatment disruption.

In radiation, our treatment quality metrics tend to be dominated by treatment plan quality and patient setup uncertainty.[12] Treatment plan quality from prior data has been well-studied, and all use the basic principle that the contoured anatomy and the relationships between normal structures and target volumes can be used to predict an expected dose distribution or dose volume histogram for the individual patient.[13,14] Then one can compare the dose in the patient's treatment plan to the prediction as a patient specific quality measure. Furthermore studies have shown that these predictions can automate the treatment planning process by including the prediction in treatment plan optimization objectives.[15] Several methods have been used such as the direct prediction of dose volume histograms from spatial relationships between critical anatomy and target volumes, to machined learning models such as knowledge based planning (KBP),[16] and artificial intelligence models such as convolutional neural networks where the goal is to predict the full 3D dose distribution.

The application of such data-driven plan quality predictions fundamentally transforms quality standards to be better tailored for each patient. One important example would be the problem of achieving near-optimal radiotherapy dose distributions through inverse optimization, that is, IMRT and volumetric-modulated arc therapy. Though IMRT and volumetric-modulated arc therapy have become the standard treatment for several cancers, the lack of systematic quality control (QC) in treatment planning has left open the possibility that the full potential of inverse optimization is not consistently realized due to human error in the generation of an unconstrained cost function. A notable study quantified the costs to planning without data-driven QC on a large-scale multi-institutional clinical trial, directly assessing the frequency and clinical severity of suboptimal treatment planning in the cooperative group setting.[17] In a secondary study of the Radiation Therapy Oncology Group (RTOG) 0126 protocol (*Phase III Study of High Dose* vs *Standard Dose in Localized Prostate Cancer*), the authors identified significant and unnecessary variations in predicted Grade 2+ late rectal toxicities with an outcomes-validated normal tissue complication probability (NTCP) model. Comparisons between the protocol plans and knowledge-based model-predicted organ doses yielded the absolute excess risk (actual NTCP − predicted NTCP) from suboptimal planning: 94 of 219 (42.9%) had ≥5% excess risk, 20 of 219 (9.1%) had ≥10% excess risk, and 2 of 219 (0.9%) had ≥15% excess risk (Fig. 3). The results of this study demonstrate that, even in the context of a multi-institutional clinical trial with centralized QA, suboptimal IMRT planning frequently put RTOG 0126 patients at a unnecessary risk of late rectal toxicities. Were they available at the time of the RTOG 0126 trial (2002-2008), the same data-driven approaches that quantified the RTOG 0126 plan quality could have eliminated these excess risks before they manifested. Such a data-driven QC approach is in fact being conducted on a currently active cooperative group clinical trial: NRG GY006 - *Radiation Therapy and Cisplatin With or Without Triapine in Treating Patients With Newly Diagnosed Stage IB2-IVA Cervical Cancer or Stage II-IVA Vaginal Cancer*. The system utilizes a validated knowledge-based planning module for cervical cancer[18] but initiates a centralized patient-specific plan quality evaluation as a pretreatment requirement for all submitting sites (Fig. 4). Critically, KBP feedback can identify unnecessary protocol deviations that can be corrected by participating sites by replanning and resubmitting the case using the KBP reference plan as guidance.

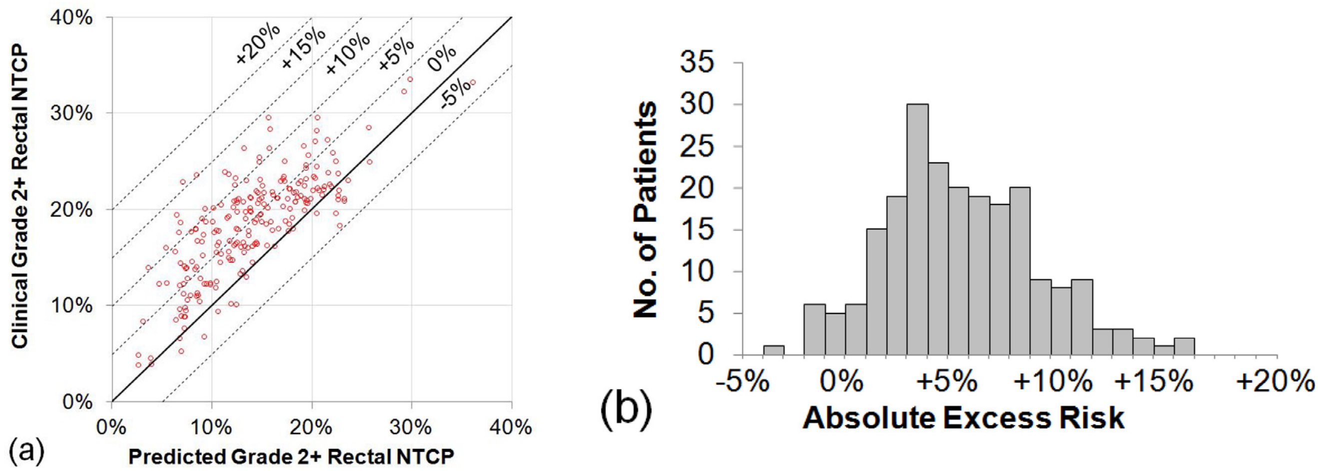


Figure 3 A secondary analysis of data from Radiation Therapy Oncology Group (RTOG) 0126 quantified excess risk of late rectal complication due to suboptimal IMRT planning. (a) Data-driven prediction of normal tissue complication probability (NTCP) vs the actual treated plans' NTCP. (b) Frequency histogram showed a mean excess risk of 4.7% ± 3.9% from actual treated plans compared to optimal plans.

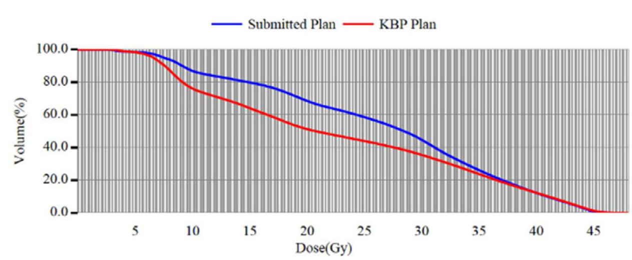
(a)

Dosimetric Analysis Summary:

Structure	NRG GY006 dose criteria	KBP feedback statement
CTV 4500	Some unacceptable deviations	Some dose metrics could likely be improved
PTV 4500	Some acceptable deviations	Dose metrics are unlikely to be improved further
Bone Marrow Act	All metrics meet protocol specifications	Some dose metrics could likely be improved
Bone Marrow	All metrics meet protocol specifications	Some dose metrics could likely be improved
Bowel	All metrics meet protocol specifications	Some dose metrics could likely be improved
Rectum	Some acceptable deviations	Some dose metrics could likely be improved
Bladder	Some acceptable deviations	Plan could be improved to meet protocol specifications

(b)

Bone Marrow Act Report



Structure: Active Bone Marrow						
Dose metric	Submitted Plan	NRG-GY006 criteria			KBP patient-specific quality check	
		Per protocol	Variation acceptable	Deviation unacceptable	KBP Plan	Knowledge-based feedback
Dmean(Gy)	24.3	≤28.5	≤30.0	>30.0	23.3	Plan meets GY006 protocol but could be improved further
V10Gy(%)	88.7%	≤90%	≤90%	>90%	74.1	Plan meets GY006 protocol but could be improved further
V20Gy(%)	59.30%	≤70%	≤75%	>75%	49.7	Plan meets GY006 protocol but could be improved further

Figure 4 Knowledge-based radiotherapy plan quality feedback on cooperative group clinical trial NRG GY006 in cervical cancer. **(a)** Overall summary scoring system gives participating sites feedback against both standard dose criteria (second column) and patient-specific factors (third column) based on knowledge-based planning results for that patient. **(b)** Each anatomical structure has an individual report, including a comparison of the submitted dose-volume histograms to the knowledge-based planning (KBP) dose-volume histograms. In this case, the submitted plan's active bone marrow (blue) is receiving significantly more radiation than expected based on the KBP result (red). This data-driven system is described extensively in Li et al.[25] (Color version of figure is available online.)

The knowledge-based analyses of these specific clinical trial examples could not be fairly described as "big data" approaches: the training/validation sets were only a few hundred cases. However, as long as the resultant QC system can produce results in real time, this form of data-driven plan QC can be scaled up with larger training sets and/or truly large databases. While the up-front costs of implementing data-driven QC represent a non-negligible investment of clinical effort and resources, the costs of not pursuing this form of quality control will be borne by the patients who are put at risk by variable plan quality. In the United States alone, approximately 500,000 patients are treated annually with radiation therapy,[19] meaning every year that passes without data-driven methods serving as patient-specific plan quality control exposes many patients to receiving treatment where radiotherapy plans have quality variations — thus exposing patients to potentially increased risks for toxicity and/or decreased probabilities for cure. These quality variations should be considered unacceptable given that there is effective parity in delivery technology, that is, everyone uses roughly equivalent delivery machines. In addition to bringing a welcome transparency to the practice of radiotherapy treatment planning, mainstream adoption of data-driven quality control would mean that every patient could experience similar high-quality care across all institutions.

One ultimate goal of delivering safe, high-quality radiation treatment is to reduce treatment toxicity. There are several efforts to use big data in the prediction of treatment related toxicities for individual patients to anticipate and/or minimize adverse outcomes. Some examples of models using clinical and dosimetric features include: weight loss prediction in head and neck cancer[20] influencing the need for feeding tubes; prediction of xerostomia[21,22]; and prediction of patient survival in patients needing palliative radiotherapy.[23] As these efforts bring real-time and clinically usable tools, models such as these will significantly improve the quality of decision making to optimize clinical care and patient outcomes.

Maintaining Up-To-Date and Relevance of Models and the Future of Implementation

As technology progresses the electronic systems for quality assurance in radiotherapy will evolve into the system depicted in Figure 1. In the beginning, we will have tools akin to spelling and grammar checkers that analyze the information against known constructs and highlight suspect items. This can be seen today in the systems evaluating dose goals for treatment plans. As we progress, these models will take advantage of the data accumulated enabling more sophisticated models to be generated and applied to the quality systems. It is anticipated that within the next decade, these systems will be commonly used in the clinic to provide oversight and guidance to help prevent errors. The functionality of these systems will continue to improve over time. Single-institution data and knowledge is likely insufficient; to fully realize the potential of using big data to improve the quality of radiation therapy and patient care, data pooling across institutions is necessary.

Systems that rely on data for quality evaluation are subject to the limitations such as suboptimal data quality and/or outdated comparison data that are no longer relevant. For this reason, proper attention to the data used, directly or in model construction, must include its relevancy in time and its quality overall. Feedback is a component of quality assurance, and in this context, new data are the feedback for continual improvement of models of quality in a learning health system. When evaluating a potential big data use, we should understand: how the system learns and improves; how new data are included in the system, and how frequently does it require model updates;[24] how does it incorporate knowledge that is not included in the data; and what is the process to keep up with the changing clinical practice to insure the safety and quality of the safety and quality system.

Summary

The field of radiation oncology is grounded in the concept that we are able to deliver safe and effective treatment to our patients. Our field has a long history of incorporating safety checks and rechecks into routine clinical practice, and fortunately significant errors are quite rare. However, when errors do occur they have the potential to cause significant harm,[25] and even successfully delivered treatment may have the potential for improvement. Thus, there is an appropriate focus on safety and quality in our field, and big data offer several promising opportunities available for detecting preventable errors that can be addressed prior to or early in a patient's treatment course. Big data can be applied at almost any level of treatment planning and delivery, and models can be developed to focus on issues big and small—from detecting millimeter inaccuracies in contours, to detecting a dose volume histogram parameter that may be able to be improved upon, to predicting meaningful clinical outcomes for patients such as weight loss and survival. The potential applications continued to expand and will significantly improve safety and quality in ways that have not been possible before. At the same time, data-driven methods are subject to misinterpretation and incorrect predictions if the quality of the data or the relevance of the selected metric is poor, and thus methods using big data have potential for harm when not applied appropriately. Thus, this burgeoning field must be approached with as much care as enthusiasm. If our field devotes the necessary attention and care to optimal utilization, big data will likely become one of the most impactful tools in our field in the decade to come.

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