



Can artificial intelligence improve cancer treatments?

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Abstract

Artificial intelligence (AI) powered by the accumulating clinical and molecular data about cancer has fueled the expectation that a transformation in cancer treatments towards significant improvement of patient outcomes is at hand. However, such transformation has been so far elusive. The opacity of AI algorithms and the lack of quality annotated data being available at population scale are among the challenges to the application of AI in oncology. Fundamentally however, the heterogeneity of cancer and its evolutionary dynamics make every tumor response to therapy sufficiently different from the population, machine-learned statistical models, challenging hence the capacity of these models to yield reliable inferences about treatment recommendations that can improve patient outcomes. This article reviews the nominal elements of clinical decision-making for precision oncology and frames the utility of AI to cancer treatment improvements in light of cancer unique challenges.

Keywords

artificial intelligence, cancer treatment, clinical decision-making, machine learning, reinforcement learning

Social media content

1. Adaptive decision support systems that continuously learn from patient data will enable the development of more effective cancer treatment strategies.

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2. The consideration of patient health state, patient stratification, outcome and toxicity predictions and AI treatment recommendations is essential to effective cancer treatment decision making.
3. Data representation and nomenclature standards will enable the creation of federated databases of clinical data to power AI-enabled decision support systems for oncology.
4. Models of data governance addressing privacy and consent challenges will unlock the value of collected patient data towards the realization of personalized, precision cancer care.

Introduction

The increasing burden of cancer on the capacity of healthcare systems and the need to reduce the negative impact of the disease and its treatment on the quality of life of cancer patients will require the development of cancer care strategies that are driven by predictive, personalized, preventive and participatory (P4) system approaches.¹ Therein lies the catalysts towards achieving the necessary effectiveness and efficiency of cancer care delivery. Currently, the most widely used treatment strategies are informed by guidelines for clinical practice developed by expert panels. For example, through its Quality Oncology Practice Initiative, the American Society of Clinical Oncology (ASCO) provides guidelines to oncology sites which in return report their practices. ASCO report back with an evaluation of the clinical site based on quality measures that focus on the process of care and patient-oriented measures such as pain management.^{2,3} However, with the increasing availability of big clinical and molecular data about cancer, artificial intelligence (AI) and machine learning (ML) are increasingly explored towards assisting in the multidimensional cancer treatment decision-making process.^{4,5} The potential utility of AI to oncology includes diagnostics, prognostications, treatment outcome predictions and treatment prescriptions. For instance, deep neural networks (DNNs) and convolutional neural networks have been used to classify skin cancer lesions⁶ and histologic patterns for lung cancer,^{7,8} predict HLA-peptide binding affinity for immunotherapy,⁹ and delineate target volume for radiotherapy.¹⁰ Other examples of ML applications in oncology include the assessment of short-term mortality risk of patients starting chemotherapy,¹¹ breast cancer treatment recommendations to prevent metastasis,¹² predictions of patients that can benefit from adjuvant therapy,¹³ and the use of Bayesian networks to assist in treatment decision-making.^{14,15} Predictions of cancer recurrence have also been made using Bayesian networks and logistic regression.¹⁶ Beyond these examples of AI application in oncology, AI may be indispensable to the future of precision oncology where the increasing number of biomarkers and treatment options being available need to be considered in light of the continuously generated streams of clinical and molecular data to identify optimal treatments that would improve patient outcomes in the face of dynamic disease-treatment interactions. Furthermore, the effective realization of adaptive therapeutic modalities to counter cancer evolutionary dynamics and therapeutic resistance¹⁷ would benefit from AI-assisted therapy design approaches that mine big clinical and molecular data for actionable knowledge to assist in the synthesis of personalized, optimal cancer treatment regimes.

The path to the realization of the AI potential in oncology is aligned with the drive for greater standardization, efficiency and consistency of cancer care across the various domains of the oncology workflow.^{18,19} This drive is best illustrated by the ongoing efforts invested towards the adoption of digital pathology^{20–23} and the use of AI in radiation oncology.^{24,25} However, there are significant challenges to the adoption of AI in the oncology clinic.^{26–29} These challenges range from the lack of data standardization and the insufficient availability of annotated data to the opacity of AI algorithms and their eventual performance drift due to the expanding cancer knowledge and data

universe.^{18,26} Furthermore, the dearth of clinical validations of AI algorithms and the lack of adequate frameworks for regulatory and legal governance of patient data and AI algorithms are also notable barriers to the wide adoption of AI models in clinical decision-making. The development of standards, guidelines and frameworks for the clinical validation of AI are among the ongoing efforts to overcome the barriers to the integration of AI in clinical practice.^{30–32} For oncology, where a tangible impact of AI use on patient outcomes is proving to be difficult to achieve,^{33,34} more research is needed to study the extent to which AI supported treatment decision-making can improve cancer treatment.

ML algorithms are fundamentally built on data-driven machine learned mappings that represent correlations or causality between variables of interest. Learned or discovered correlations and patterns from big data are the basis for inferences, predictions, prescriptions and recommendations made by AI/ML algorithms. For non-safety critical applications such as image recognition, movie recommendations, market segmentation or trivia games, the use of AI has been very effective in mobilizing the statistical power of big data towards solving the problems at hand. On the other hand, replicating the success of AI to treatment decision-making in oncology has so far been elusive.^{33–36} Machine learned or discovered statistical correlations between treatments and patient outcomes are inevitably limited in their predictive power due to the reliance on temporal snapshots of tumor dynamics associated with treatment response data of the relevant patient population. Indeed, the heterogeneity and evolutionary dynamics of cancer^{37–39} can potentially make every newly diagnosed cancer sufficiently different from the machine learned statistical patterns for the AI algorithms to yield reliable inferences about treatment recommendations that can improve patient outcomes. In particular, the static data context of machine learning imposes an intrinsic limitation on the capacity of ML models to recapitulate the nonlinear, time-varying dynamics of patient treatment response. Furthermore, the longitudinal nature of cancer care requires AI algorithms to be adaptive to the inevitable changes of the tumor pathophysiology which occur during the multiple cycles of treatments administered in the neoadjuvant, curative, adjuvant, management and relapse settings. In light of cancer unique challenges that are highlighted above, further research is needed to chart feasible pathways towards realizing AI potential utility to cancer treatment decision-making.

Foundations of cancer treatment decision-making

The expanding universe of therapeutic options and the availability of growing clinical and molecular datasets about cancer are prime ingredients for realizing the vision of an AI-supported personalized, precision oncology. The potential utility of AI may be leveraged towards the development of an adaptive cancer treatment framework that addresses cancer evolutionary dynamics, which underlies therapeutic resistance as the most critical challenge in the fight against cancer. The conception of such framework is inspired by the vision of rapid learning health care systems,^{2,40,41} where routinely collected and analyzed patient clinical and omics data can provide a constant source of updated clinical evidence to support the continuous improvement of treatments and patient health outcomes. Adaptive cancer treatment approaches require the integration of three canonical components of effective clinical decision-making:

- Modeling disease state dynamics
- Prediction of treatment outcomes and toxicity
- Adaptive treatment recommendations

The consideration of the above-mentioned elements addresses key challenges associated with the complexity of decision-making in oncology.⁴² The structure of this nominal, clinical decision-making framework supports the inclusion of decision factors and criteria associated with the physician, the patient and the context of the oncology practice which are usually considered in making clinical decisions.⁴² These decision factors include patient disease features, biomarkers, treatment toxicity, treatment outcomes, patient quality of life, treatment protocols and guidelines, and physician experience. The consideration of tumor evolutionary dynamics through the modeling of disease state stems for the growing understanding of the determinant role that evolution has in the progression of cancer^{43,44} and the necessity to operationalize such insight to steer cancer dynamics away from therapeutic resistance.⁴⁵ The regular monitoring and prediction of tumor evolutionary dynamics would enable the synthesis of adaptive treatment recommendations that are personalized to the specific features of the patient's disease and its progression dynamics.

Artificial intelligence-enabled adaptive cancer therapy

Cancer clonal evolution fuels tumor evolving genetic heterogeneity underlying therapeutic resistance. Mathematical models estimate the existence of 1–4 dominant clones at frequencies greater than 10% at the time of tumor detection for colorectal cancer, whereas most subclones are present at frequencies that are below 10%.⁴⁶ In order to mitigate the evolution of therapeutic resistance, treatment decisions would have to be cognizant of the intra-tumor clonal heterogeneity and the evolution of subclonal populations, including those that are not detectable at the time of diagnosis. Noting that therapeutic resistance is driven by the proliferation of pre-existent resistant subclones, evolutionary-based treatment strategies, such as adaptive and extinction therapies, have been proposed to steer the evolutionary dynamics of resistance towards cancer cure or management.⁴⁵ Adaptive therapy exploits the competition between treatment-resistant and treatment-sensitive clones, whereby therapy cycles aim to maintain a proportion of treatment-sensitive cancer cells that compete against treatment-resistant ones towards perpetuating a manageable disease burden. On the other hand, extinction therapy exploits the vulnerability of small populations to ecological perturbations. In a first stage, cycles of a selected therapy targets treatment-sensitive clones reducing the disease burden to clinically undetectable small residual populations of resistant clones. A second therapy is applied as a 'second strike', before a clinically detectable rebound of resistant clones, to perturb their small populations and drive them to extinction. Both adaptive and extinction therapies are inspired by eco-evolutionary models and have the advantage of relying on actionable yet simple principles. However, their clinical implementations face multiple challenges. These include managing treatment toxicity and obtaining sufficiently accurate predictions of disease burden throughout the duration of patient care, from diagnosis and initial treatment to disease management. Furthermore, given the increasing numbers of cancer biomarkers and treatment agents being available, and the complexity of treatment-response dynamics, designing patient-centric, personalized eco-evolutionary treatments will be challenged by the human cognitive capacity, shown to handle no more than five variables for decision making.⁴⁷ Adaptive and extinction therapies can be framed as a sequential decision problem.⁴⁸ Both therapies involve successive selections of treatments to be administered, based on monitored tumor burden, towards achieving a desired objective, which may be cure or disease management. Reinforcement learning^{49,50} is a potentially effective AI approach for the selection and sequencing of therapeutic agents within the context of adaptive cancer therapy. Given a continuously observed disease state, the goal is to select a sequence of treatments to drive the cancer to a terminal state, such as remission, while optimizing a reward function defined based on treatment outcomes and toxicity. In the parlance of reinforcement

learning, the treatment decision-maker is labelled as the agent acting on the cancer, as the environment, through the administration of a sequence of treatments where each treatment is selected based on the observed state of the cancer while maximizing a cumulative reward function for the actions of the decision-maker (i.e., the agent). The reward can be defined as a function of data-driven predictions of treatment toxicity and outcomes so as to guide treatment selection towards the goal of improving overall survival with minimal treatment toxicity as a clinical end-point.

Disease state modeling

Cancer is a stochastic, nonlinear dynamical system whose treatment requires a regularly updated observation of disease state as a feedback for therapy adaptation to its complex treatment response. Reinforcement learning approaches to treatment selection involves a feedback loop that adapts the therapy based on a reward obtained for selecting a specific treatment when the disease is observed in a given state. The reward function can be defined to guide treatment selection based on the expected treatment outcomes and toxicity as the most meaningful clinical end-points.

Although cancer progression dynamics under therapeutic interventions are stochastic, it is reasonable to categorize them along a finite set of disease states. RECIST (response evaluation criteria in solid tumors) categorization of tumor burden in response to treatment⁵¹ provides a nominal template for the definition of disease states. However, a fine-grain disease state definition may be needed to improve the monitoring resolution of tumor dynamics, in particular with respect to clonal composition of the tumor. Each one of the RECIST categories, i.e., SD (stable disease), PR (partial response), CR (complete response), and PD (progressive disease), can be expanded into multiple substates to reflect fine-grain properties relevant to tumor evolutionary dynamics, including clonal composition. Clinically parameterized mathematical models of tumor evolutionary dynamics could provide additional guidance on how to define the set of disease states that would be appropriate to represent the key stages of the disease.

The feasibility of adaptive cancer treatment depends on advances in disease monitoring and assessment approaches of treatment response.^{52–56} Although RECIST guidelines can serve as a nominal tool for the evaluation of patient response to treatment, continuous monitoring of the tumor and its microenvironment is needed to assess the effect of therapy on tumor progression dynamics. Imaging provides an avenue for the assessment and quantification of physiological and molecular tumor features. The combined use of MRI (Magnetic Resonance Imaging), PET (Positron Emission Tomography), and CT (computed tomography) imaging modalities, is enabling the quantification of tumor heterogeneity and the estimation of its properties, including: diffusion, glucose metabolism, hypoxia, T cell infiltration, and cellularity.^{53,54,57,58} Imaging-based parameters quantifying tumor properties have been shown to have either pre-clinical or clinical prognostic information^{53,59–62} and hence may be used to resolve the fine-grain substates within the RECIST categories. In addition to the imaging-based estimation of tumor burden, advances in liquid biopsy techniques^{56,63} used to extract circulating tumor cells (CTC), and circulating tumor DNA (ctDNA) from patient blood are paving the way for feasible approaches to the estimation of tumor clonal composition.⁶³ In fact, the longitudinal monitoring and estimation of disease states using liquid biopsy is expected to be a key enabler of adaptive cancer therapy. Finally, proxy biomarkers such as PSA (prostate specific antigen) for prostate cancer and lactate dehydrogenase for melanoma, which have been used to measure tumor volume,¹⁷ may also be combined with the above-mentioned estimation approaches to yield more accurate inferences of observed cancer disease states.

Big data infrastructure

An AI-enabled framework for adaptive cancer therapy would involve AI models for treatment recommendations and predictions of treatment response and toxicity. The training of these AI models is dependent on the availability of quality clinical, molecular and imaging data in sufficient volume. The training data must exhibit a high signal-to-noise ratio and must be sufficiently accurate and representative of the diverse patient populations in order for these AI models to achieve their optimal performance and applicability in the clinic. Data relevant to precision oncology include multi-omics data (e.g. imaging/radiomic, proteomic, genomic, metabolomic, etc.) in addition to pathology data, electronic medical records (EMR), as well as epidemiological and clinical trials' data. Although big genomic, transcriptomic, proteomic and epigenomic datasets spanning multiple cancer types are publicly available to researchers through the cancer genome atlas (TCGA) program,⁶⁴ most patient data are not accessible outside the institutions where the data are collected. This applies to clinical data that are being continuously accumulated in EMR systems across hospitals and clinics around the world. Access to these protected treasure troves of data about cancer is critical to the development and assessment of AI-enabled applications for cancer treatment decision-making. One of the primary challenges to patient-level data sharing between institutions is the compliance with data privacy and protection regulations such as the General Data Protection Regulation (GDPR).⁶⁵ Data interoperability, both syntactic and semantic is another challenge to the development of clinically useable AI-enabled applications to support cancer treatment decision-making. In this respect, the independent collection of clinical data at points of care would need to adhere to inter-institutional standards of interoperability to facilitate data exchange, sharing and harmonization across organizations. The recognition of this need has led to the emergence of a growing body of standardization initiatives,^{66,67} including the completed Clinical Data Standards Initiative.⁶⁸ These standards are expected to serve as the backbone for the integration of data streams from external EMR systems and other systems/databases covering distinct aspects of disease diagnostics, treatments, and patient outcomes. Indeed, the interoperability expected from the adherence to these data standards is a prerequisite to achieving the much-coveted overall goal of health data integration.⁶⁹ The integration of multi-modal cancer data is another challenge to unlocking the utility and value of clinical, molecular and imaging data in powering AI-enabled adaptive cancer treatments. Several approaches have been proposed to fuse the disparate types of cancer data, including the reliance on abstractions that can bridge and harmonize data covering distinct knowledge spheres such as diagnostics and proteomics.⁶⁶

The computational burden of training and optimizing DNNs or deep learning (DL) models increases with the product of the size of the training data and the number of model parameters. This has raised the concern that computational limits would constrain a variety of DL applications.⁷⁰ On the other hand, maximizing the predictive power and clinical relevance of DL models for applications, such as the prediction of cancer therapy response, will benefit from the availability of large-scale datasets.⁷¹ In light of the concern about the scaling of computational burden as a function of the number of data points, the exploitation of an expanding patient data space towards highly performing AI models that are useable in the clinic would have to also consider the ensuing computational needs.

Overcoming the challenges in the collection and sharing of quality patient data in sufficient volume would unlock the "ground-truth" knowledge necessary to develop and assess the predictive power of AI models for precision oncology.⁷² Ultimately, realizing the AI potential in healthcare, including oncology, will require building collaborations among the relevant stakeholders to

establish big data infrastructures to collect, curate and share the quality data needed to develop clinically pertinent AI applications.^{67,73}

Is there a pathway to artificial intelligence enabled improvement of cancer treatments?

The application of reinforcement learning to adaptive cancer treatment is congruent with the therapy objective of achieving an effective control of disease course with the end-goal of cure or chronic care management. The feasibility of the approach does however hinge on a precise monitoring of the disease state. Furthermore, although reinforcement learning algorithms need the latitude to explore and learn from the response to a diverse set of actions, such exploration is not feasible in cancer care. The set of available treatments and combination thereof that can be utilized as therapeutic actions in a reinforcement learning algorithm, or any other adaptive treatment approaches, must have prior clearance for clinical use. On the other hand, the set of clinical trials for combination therapy however large and growing it may be, it would still be limited in covering the space of possible treatment combinations that could be explored by reinforcement learning. Therein lies the conundrum. Although AI algorithms such as reinforcement learning have the potential to find the optimal sequence of cancer treatments for a specific patient, learning is required through exploration, which has to be curtailed to avoid complex toxicity to the patient. However, an adaptive treatment designed to incorporate a controlled exploration of an approved set of treatment options may be sufficient for patient-centric personalization of the therapy. Lung cancer may be a good illustrating example to consider given the many ongoing or completed clinical trials on the combined use of targeted therapies, chemotherapy, and immunotherapy in the neoadjuvant (i.e., before surgery) and adjuvant (i.e., after surgery) settings for respectable stages IB to IIIA NSCLC (Non-small cell lung cancer). Ongoing or completed clinical trials on TKIs (tyrosine kinase inhibitors) as adjuvant therapy for resected IB to IIIA NSCLC involve the use of different agents (e.g., Erlotinib, Gefitinib, Vinorelbine and Cisplatin) administered for a mean duration that ranges from 4.8 months to 23.9 months.⁷⁴ There are other ongoing or completed clinical trials such as NAUTIKA1 (NCT04302025) on the use of Alectinib, Entrectinib, Vemurafenib, Cobimetinib as neoadjuvants before resection, followed by chemotherapy and Pralsetinib as adjuvant therapies for NSCLC. Other clinical trials are also ongoing or completed on the use of combinations of chemotherapy and immunotherapy (PD-1/PD-L1 antibody) for NSCLC in the neoadjuvant setting.⁷⁵ After the approval of Osimertinib⁷⁶ as an adjuvant therapy for EGFR mutated NSCLC, the NeoADURA (NCT04351555) study was initiated on the use of Osimertinib alone or in combination with chemotherapy as a neoadjuvant for NSCLC. These studies are expected to generate an extensive amount of data to guide the choice of combination therapies that can be used preoperatively and postoperatively for resectable NSCLC. AI-powered analytics would be most appropriate to mine the increasingly accumulating data from these clinical trials to support oncologists in streamlining the process of selecting candidate therapies to be used in the neoadjuvant and adjuvant settings based on biomarkers such as the status of oncogenes (e.g., EGFR, ALK, and RET) for targeted therapy and the status of PD-1/PD-L1 for immunotherapy. Example AI approaches that can be used in this case could include probabilistic decision trees, which yield recommendations that are explainable and hence more trusted by oncologists. While the design of core therapeutic strategies for patients is unlikely to rely on AI beyond the use of this latter as an off-line support tool, there is a high utility potential for the use of AI approaches such as reinforcement learning to control residual disease and acquired resistance within an adaptive therapy framework. Indeed, a designed treatment for an NSCLC patient which may include a neoadjuvant immunotherapy combined with

chemotherapy (e.g., Nivolumab with Platinum chemotherapy) followed after surgery with Osimertinib as an adjuvant therapy, will need to be complemented with additional decisions about the optimal duration of adjuvant therapy and the subsequent treatments necessary to deal with residual disease and acquired resistance. These treatment decisions may be driven by a reinforcement learning approach that adapt adjuvant treatment to achieve long-term remission based on disease state monitoring using ctDNA-based liquid biopsy techniques. Assuming a slow evolution of the disease at this stage of care for the cancer patient, it may be clinically safe to extend more latitude for reinforcement learning to explore the use of a larger set of therapies applied at the minimum effective dose. However, this will require a continuous monitoring of disease state using ctDNA, including the inferencing of clonal composition of minimal residual disease, which would serve as an early warning tool against potential recurrence. Disease state feedback will also enable the AI-based adaptive treatment to maintain a one-step ahead control of the disease. The reward function of the reinforcement learning approach would in this case be defined based on the overall objective of the adjuvant therapy. For instance, the choice to manage cancer in the face of acquired therapeutic resistance may require the adoption of an evolutionary based approach that leverages clone competition.¹⁷ In such ‘clone wars’ setting, the reward of reinforcement learning may be defined as a function of clone frequencies so as to maintain the cyclical stability of the lesion’s clone composition and its therapeutic responsiveness.

Realizing the expected utility of AI as a catalyst for the improvement of cancer treatments will ultimately require clinical trials on the use of adaptive treatment approaches in order to identify the principal patterns of an effective and safe adaptive therapy. Insight gained from mining clinical trials’ data about traces of AI recommended treatments, trajectories of disease states, and patient toxicity are expected to guide the convergence towards clinically effective and safe sets of treatments and combination thereof to power AI-enabled adaptive cancer therapy.

Conclusions

The rapidly accumulating clinical and molecular data about cancer has fueled the expectation that AI powered by this big data would revolutionize cancer treatment decision-making. Recent projects that explored potential applications of AI in precision oncology has shown that cancer treatment presents unique challenges that are not easily overcome by machine-learned statistical models of the disease. An exploration of these challenges points to the potential utility of AI as a catalyst in the conception of a framework for adaptive cancer therapy. The framework would exploit continuously updated data-driven clinical evidence towards more effective treatments of cancer. In particular, the use of reinforcement learning to drive adaptive adjuvant therapy may be clinically feasible under the assumption of slow evolution of the disease and a continuous monitoring of its course using ctDNA-based biopsy techniques. However, clinical trials on the use of adaptive treatment approaches in cancer care will ultimately be needed to crystalize the parameters and modalities of an effective and safe AI-enabled adaptive cancer therapy.

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