Trends in General Medicine

Artificial Intelligence Revolutionizing Cancer Care: A Comprehensive Overview

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ABSTRACT

Artificial intelligence (AI) is rapidly developing in the field of healthcare. It is expected to play a key role in oncology, in the areas of diagnosis, treatment, but also screening and cancer research. AI has evolved from a specialized resource to a readily accessible tool for practitioners and cancer researchers. AI can thus facilitate the screening, early and accurate diagnosis of cancers. Thus, the computer analysis of medical images in particular, radiological (radiomics), or anatomo-pathological (pathomics), has shown many very interesting results for the prediction of prognosis and response of patients with cancer. Thanks to deep learning algorithms, AI can identify subtle patterns on medical images, such as X-rays, MRIs or CT scans, that are likely to escape the human eye. In terms of treatment, AI can contribute to the development of personalized treatment plans. By analyzing large datasets, which can predict tumor response to certain treatments. AI also plays a key role in patient monitoring. AI-based systems can continuously monitor patients' health status, detecting any recurrences or complications. In the field of cancer research, AI-based tools can boost research productivity in daily workflows, but they can also extract hidden information from existing data, enabling new scientific discoveries. Researchers working in traditional biological sciences can use AI-based tools through commercially available software, while those who are more inclined to computer science can develop their own AI-based software pipelines. In this article, we will provide an update on the contribution of AI in the field of oncology, the practical applications already validated and the perspectives of this tool.

Keywords

Artificial Intelligence (AI), Cancer, Medical oncology, Surgery, Radiation therapy, Pathomics, Radiomics, Screening.

Introduction

Artificial intelligence (AI) is defined as "a system that works through a machine that, in order to meet a given set of human-defined objectives, is capable of making predictions, recommendations, or decisions that affect real or virtual environments" [1]. In oncology, the collection of information or **BIG DATA** is a very important concept, which constitutes a basis for understanding the mechanisms of carcinogenesis, signaling pathways, and therefore identifying therapeutic targets, but also for defining the profiles of populations at risk and therefore guiding cancer screening and prevention strategies. The generation and structuring of an exponential number of data in oncology has constituted a solid foundation for the development of artificial intelligence (AI) tools in oncology. Indeed, there is no AI without large-scale data collection and analysis. This massive data or big data is a set of extremely large, potentially complex, multidimensional, unstructured data, which can come from heterogeneous sources (clinical, biological, social or environmental) and accumulate quickly [2]. The considerable amount of information thus generated has created new challenges to be met, such as storage, processing and even exploitation of information.

AI has made it possible to rapidly analyze this data, and has become a powerful ally in the fight against cancer by facilitating therapeutic decision-making and predicting the toxicity of certain treatments [3], but also by offering predictive medicine that has improved the results of cancer screenings and in particular interval cancers [4,5] but also in other areas such as surgery, radiotherapy and anatomical pathology [6-8].

Impact of AI for Decision Support in Medical Oncology

AI has the ability to provide an integrated analysis of large, complex, multiparametric, and high-dimensional datasets, and is therefore particularly well-suited for cancer molecular data. The indications for DNA and RNA sequencing of cancers have increased massively in recent years, and the results of these analyses are a major factor in therapeutic decision-making, particularly in advanced situations. These databases have made it possible to develop AIbased tools for theranostic purposes, allowing for the definition of a better therapeutic strategy for the patient. For example, AI tools based on genomic and transcriptomic data have been created to predict sensitivity to radiotherapy [9], chemotherapy, or immunotherapy [10]. The SHIVA01 study has developed tools to prioritize the results of molecular analyses and help choose the most appropriate targeted therapy in case of multiple alterations, thus improving precision medicine, improving progression-free survival and overall survival of patients with cancer [11].

One of the examples of AI-based tools that has revolutionized therapeutic decision-making in oncology is TransCUPtomics, which makes it possible to identify the primary tumor in cases of "cancers of unknown primary" or CUP [12]. Indeed, these tumors are characterized by the presence of metastases in the absence of a primary identifiable by standard diagnostic means, treatment is based on broad-spectrum chemotherapy of limited efficacy. In recent years, multiple AI tools have been developed to predict the tissue of origin of CUPs and guide systemic treatment. These tools have been based on the analysis of different types of data, including digital pathology, genomic data, transcriptomic data, and methylomic data [8-13]. TransCUPtomics is a deep learning tool trained on transcriptome sequencing (RNAseq) data from

over 20,000 tumor and normal tissue samples and is able to predict the tissue of origin of a CUP in nearly 80% of cases based on its RNAseq profile, it has also made it possible to guide first-line treatment in 73% of patients, with partial or complete responses observed in most patients [12].

Example of AI's contribution to the evaluation of treatment efficacy and therapeutic decision-making the Sammut et al. study concerns the evaluation of predictive criteria for the effectiveness of neoadjuvant chemotherapy for breast cancer [14]. This study included 180 women with different forms of breast cancer requiring neoadjuvant medical treatment. The treatment was based on chemotherapy combining a taxane and an anthracycline. Patients whose tumors were HER2+ received three cycles of anti-HER2 therapy in combination with a taxane. At the end of neoadjuvant treatment, the therapeutic response is classified according to the RCB score. The analysis combines clinical, genomic and transcriptomic parameters, as well as the study of tumor infiltration by immune cells (Figure 1). The variables associated with clinical response are then filtered by univariate selection and collinearity reduction (for precision Univariate selection allows to identify the variables associated with prognosis. Collinearity reduction allows to limit the weight of the variables that are highly correlated with each other, which would bring redundant information to the model), and then used to build a classifier using three algorithms: logistic regression, support vector machine and random forest [14].

The study suggests that response to therapy is determined by the initial properties of the entire tumor ecosystem, which can be captured through data integration and machine learning. This approach has the potential to be applied to develop therapy response predictors for other cancers as well.

This study is one of the first to introduce the concepts of machine learning brought by artificial intelligence to help us extract the most important predictive markers for the effectiveness of neoadjuvant chemotherapy for breast cancer.

Despite the performance of these machine learning models for neoadjuvant treatment response compared to those based on clinical variables, this classifier remains imperfect and the integration of other parameters, such as those provided by the transcriptome or tumor section imaging, should improve the prediction of treatment response and feed the decision tree.

Another major application area of AI in oncology is the prediction of potential side effects associated with cancer treatments and therefore anticipating complications and adjusting treatments.

The creation of AI tools aimed at predicting the risk of toxicity of radiotherapy in various types of cancers based on machine learning algorithms [15], or of different systemic treatments, such as anthracyclines in breast cancers or the sequelae of polychemotherapy used in pediatric cancers [16].

AI can also revolutionize the design of new anticancer drugs by



Figure 1: Multi-omics data in neoadjuvant chemotherapy-treated breast cancers.

A. Left: Schematic representation of the management of a patient in the context of a neoadjuvant chemotherapy protocol. Right: Representation of the tumor immune microenvironment and representation of the activation of a T lymphocyte by an immune checkpoint inhibitor (ICI) drug. B. Integration of data into machine learning models to define a personalized therapeutic approach and predict treatment response. DC: dendritic cell; MDSC: myeloid-derived suppressor cell; CAF: cancer-associated fibroblast; WES: whole exome sequencing; sWGS: shallow whole genome sequencing; RNAseq: RNA sequencing. (D'après Gorvel L, and al Artificial intelligence contribution to multi-omic data in the treatment of breast cancers by neoadjuvant chemotherapy. Med Sci (Paris). 2022 Oct; 38(10):772-775.)

creating potential molecular structures and predicting their efficacy before even synthesizing them. Notably thanks to generative AI, which is a branch of AI focused on the creation and generation of new and realistic data, rather than simply analyzing or interpreting existing data [17]. This procedure consists of several steps [18], namely first of all data collection and preparation, development of machine learning algorithms, but also generation of new potentially active molecular structures against cancer.

AI will also allow for the filtering and selection of molecules based on criteria such as pharmacological properties, feasibility of synthesis, stability and potential toxicity; and "in silico" validation: that is to say the carrying out of simulations and tests to predict the activity and interaction of new molecules with cancer cell targets as well as their toxicity [16-18].

AI also makes it possible to synthesize the selected molecules and test them in the laboratory on cell cultures or animal models. Finally, thanks to its power of continuous learning, AI makes it possible to use the results of experimental tests to refine the algorithms and generate even more effective molecules [15,16].

An example of a promising molecule that has benefited from generative AI for its creation is RLY-4008, an irreversible selective oral FGFR2 inhibitor, with objective responses observed notably in cholangiocarcinoma with FGFR2 alterations, including after resistance to other anti-FGFRs [19].

Artificial Intelligence and Cancer Surgery

In recent years, cancer surgery has seen the arrival of multiple instruments and practices related to artificial intelligence. Two areas in particular have evolved rapidly: first, the materials used in the operating room, and then predictive tools concerning the results of surgical procedures, both in terms of operability and oncological results, but also in terms of the risk of complications and optimization of safety in the operating room.

Intraoperative imaging: This often involves intraoperative imaging to distinguish healthy tissue from tumor tissue or, thanks to navigation systems, to be able to operate with navigated instruments in complex anatomical areas through minimally invasive routes within noble organs to be spared, all in real time [20].

Augmented reality: Unlike simulators, augmented reality (AR) allows images to be superimposed on the structures during operations, whether open or minimally invasive procedures (such as laparoscopy or robotic surgery). It is now possible, for example, to create images of the liver using stereoscopic reconstruction of the surface and semi-automatic registration in combination with deep learning to obtain 3D intraoperative AR images [6,21]. However, the design of organs that deform or simply move with breathing (such as the heart, lungs or liver for example) is much more complex than bone structures. Indeed, multiple factors intervene in the prediction of the movement or deformation of these organs.

Predictive tools: AR combined with AI in the operating room, allows to generate decision algorithms based on the accumulation of data from thousands of patients allow to offer preoperative predictive tools [22], or even intraoperative ones on the probabilities of success or risks of complications of the procedure considered. These tools offer real-time feedback during surgery, alerting the surgeon to potential incidents or suggesting alternative approaches based on the evolving situation [23].

The Roles of Artificial Intelligence in Cancer Anatomical Pathology

Cancer anatomical pathology, which combines the analysis of the morphological and molecular characteristics of tumors, is benefiting from a strong dynamic on technological developments linked to AI, particularly in the field of AI image analysis, or computer vision [24].

Image analysis and diagnosis: The evaluation of histological images can sometimes be subjective and quite variable depending on the case. AI can improve the standardization and accuracy of diagnoses on tumors. By using different databases, AI can learn both to classify tumors, the example of breast and lung cancer [25-27], to perform theranostic scores, it can be for example the automated reading of anti-PD-L1 immunohistochemical markers [28], anti-HER2 [29], the evaluation of tumor proliferation by

counting cycling cells or mitoses [30]; AI can also perform tasks that are impossible for the pathologist with a microscope, such as predicting mutations on a simple standard histological slide [25]. Thus, AI will allow tomorrow the advent of a real "augmented pathology", enriching the path of precision and personalized oncology [25].

Virtual slides analysis: Thus, the computational analysis of virtual slides has recently been evaluated for the optimization of histological or cytological diagnosis, the prediction of the prognosis or the genomic profile of cancer patients [24,31].

Deep learning and beyond: However, the contributions of AI go further than simple diagnostic assistance, in particular deep learning, the founding first publication of which dates back only to 2015 [32]. Deep learning thus makes it possible to predict molecular signatures from simple routine histological slides. The first applications in the field were the prediction of microsatellite status [33], mutations and fusions in lung adenocarcinomas [26] or tumor mutational burden (TMB) [34]. In terms of prognosis assessment, AI is able to detect morphological criteria invisible to pathologists, which will make it possible to predict the prognosis of a cancer, independently of clinical criteria [35].

Artificial Intelligence in Radiotherapy Oncology

Radiotherapy oncology combines the clinical aspect of oncology with the increasingly complex technicality of radiotherapy. The clinical aspect lies in the study of the patient's prognostic clinical, radiological and histological factors in order to establish the indication for radiotherapy. The technical aspect involves an entire chain involving several healthcare professionals in several stages in order to arrive at a personalized treatment plan. These steps are time-consuming and can sometimes lack precision. AI can therefore intervene in two stages; first to make the technical chain of treatment design and implementation more efficient and faster, as well as to help in the implementation of therapeutic strategies. For a given therapeutic strategy, these models would allow a better estimation of the benefit-risk ratio for a given patient. The potential applications of AI in radiotherapy are therefore very numerous, such as the prediction of prognosis or response to treatment, the prediction of toxicities, the acceleration of patient care and the harmonization of practices with for example automatic delineation, automated planning or the creation of artificial scanographic images [36].

Synthetic Imaging for Simulation and Adaptive Radiotherapy Among the applications of AI to the field of radiotherapy is Synthetic imaging for simulation and adaptive radiotherapy. Indeed, the use of a simulation scanner makes it possible to define the treatment position and obtain the patient's density mapping in order to be able to simulate dosimetry. However, there are many situations where the use of an MRI superimposed on the scanner will be necessary in order to be able to carry out the delineation. The use of deep-learning algorithms has made it possible to achieve this objective and some models have received validation from the Food and Drug Administration (FDA). The most frequently used algorithms are U-Nets, and more recently Generative Adversarial Networks (GANs) which are trained by combining a synthetic image generator and a discriminator, which will be able to distinguish a synthetic image from a real image [37].

Automatic Delineation

Another implication of AI in the field of radiotherapy is Automatic delineation which is a promising process for optimizing radiotherapy. It saves medical time and reduces inter-observer variability in the delineation of target volumes and organs at risk (OARs). The evaluation of automatic delineation solutions is based on geometric indicators and on the time saved compared to a manual approach. Several commercial solutions are already available for OAR delineation, and some include the delineation of certain consensus target volumes. S.P. Primakov et al. developed an automatic delineation model for primary lung tumors using the centering CT scan and a PET scan [38]. Automatic delineation of more personalized target volumes, such as tumors, is an active area of research with encouraging results. The widespread adoption of automatic delineation could improve the efficiency, accuracy and standardization of radiotherapy treatments [38].

Decision Support and Indication for Radiotherapy

Finally, in terms of medical decision support and indication for radiotherapy, AI can make it possible to develop radiomic signatures, which can then be used to guide a therapeutic strategy. R. Sun et al. tested a radiomic signature on 3 cohorts with maintained performances, in order to predict without biopsy the lymphocytic infiltration of metastases [39]. AI can therefore have a role to better predict the response to an oncological treatment for each of the known lesions and to indicate a local strategy such as radiotherapy to eliminate sites at risk of resistance. In localized cancers, radiotherapy has become an alternative to surgery for organ preservation, however predictive tools would make it possible to better select patients who would benefit from it. J.E. Bibault et al. developed a predictive signature of complete response in patients with rectal cancer [40]. This type of model could help select patients eligible for rectal preservation after a complete response to neoadjuvant treatment.

Artificial Intelligence and Cancer Screening: The Breast Cancer Model

The contribution of artificial intelligence in cancer screening has taken on significant momentum in recent years in several locations, including the lung [41], the colon [42], the skin [43], but also in the early detection of pancreatic cancers [44]. The contribution of AI in cancer screening is more advanced in breast cancer, with several studies carried out and applications already on the market [5,45].

Artificial intelligence applied to mammography aims to improve the interpretation of radiologists. Several types of uses of artificial intelligence are now declining in the practice of screening mammography. First of all, many artificial intelligence solutions have been developed to improve the image quality-toradiation dose ratio [46]. These solutions have been developed with the aim of reducing radiation exposure. Some of these

solutions relate to the primary reconstruction system and are focused on optimizing the signal-to-noise ratio, others on optimizing patient positioning (in particular by improving breast compression, responsible for 75% of the radiation dose) [47]. The latter also have the advantage of improving the Work-Flow by creating a "Technically Insufficient Image (CTI)" alert for the operator, which allows the image to be retaken immediately instead of waiting for the radiologist's request [48].

A lot of work is being done on the ability of artificial intelligence to go beyond radiological information that can be understood by humans and to try to better define the level of risk of each woman in order to better adapt her follow-up (type and rhythm) (Figure 2), example of Mammorisk, which is a computer screening tool that allows calculating the individual risk of developing breast cancer within 5 years [45]. Thus, a lot of work is being carried out to test predictive models based on deep learning models applied to mammography in comparison with the conventional models used today [49].

However, the path to large-scale clinical adoption of AI is not without obstacles. The main challenges include the clinical validation of the effectiveness of the algorithms, the guarantee of their robustness in the face of varied data sets, the fight against the mystery of the "black box" of AI, and navigation in the complex terrain of regulatory, legal and economic considerations. In addition, it is essential to address potential biases, particularly those that negatively affect minority populations, and to evaluate the performance of AI systems using reliable measures to build fair and trustworthy tools [50].

Artificial Intelligence in Healthcare Practices: Ethical Issues

The question of the place of ethics in the development of AI is increasingly being invited into debates: reliability, protection of rights and freedoms, responsibility, transparency of systems, human-machine relationship.

It is also essential to clarify medical responsibility when using diagnostic, advisory or support solutions. To date, in the event of a fault or breach, legal responsibility lies with the doctors or caregivers in charge of the patient. In the case of algorithms or intelligent robots, there is as yet no clear legal framework (no autonomous legal personality of the machine), making it possible to attribute responsibility to the designer of the solution, in the event of errors or hazards.

WHO's guiding principles

In 2021, WHO published the first global report on artificial intelligence (AI) applied to health and six guiding principles for its design and use [51]. The report on the ethics and governance of artificial intelligence in health (entitled in English: Ethics and governance of artificial intelligence for health) is the result of two years of consultations conducted by a group of international experts appointed by WHO. This report enshrines a set of major ethical principles. WHO hopes that these principles will serve as a basis for governments, technology designers, businesses,



Figure 2: Diagnostic flow chart of breast cancer and application of artificial intelligence [50].

Potential application of AI in the diagnostic workflow of patients with breast cancer. IC = interval cancer; MMG = mammography; DBT = digital breast tomosynthesis; USG = ultrasonography; MRI = magnetic resonance imaging; LN = lymph node; SLNB = sentinel lymph node biopsy; W/U = workup; CR = complete remission; PR = partial response; SD = stable disease; PD = progressive disease; AI = artificial intelligence.

civil society and intergovernmental organizations to put artificial intelligence at the service of health in an ethical manner. According to this document, the Great ethical principles governing the use of artificial intelligence for health are: Protecting human autonomy; promoting human well-being and safety and the public interest; ensuring transparency, explainability and intelligibility; fostering responsibility and accountability; ensuring inclusiveness and equity and promoting AI that is responsive and sustainable [51].

While accepting and supporting the logic of progress, a state of vigilance is essential. This vigilance also meets the demand for scientific rigor aimed at evaluating the risk-benefit balance of all things and at validating and retaining only what brings something positive, and an improvement in the quality of life or survival for patients.

Conclusion

Artificial intelligence (AI) in oncology is a great hope due to its ability to compile a large amount of data and emit relevant diagnostic and therapeutic hypotheses, allowing the development of personalized medicine. AI is the set of theories and techniques used to create machines capable of simulating intelligence.

In cancerology, its applications are found in many areas: epidemiology, screening, treatments, patient monitoring. The main

applications today:p redict risk and survival, automate radiotherapy treatments and improve patient monitoring.

AI has significant potential to improve practices in oncology, whether in terms of diagnosis, prognosis, theranostics, or even in the design of new anticancer treatments. Although there is not yet intensive use of AI in the clinical practice of medical oncologists, unlike other specialties such as radiotherapy and anatomical pathology, there are nevertheless a great many research programs and tools under development that could enter routine in the near future, as was the case for the TransCUPtomics tool.

The integration of AI into cancer care redefines our approach to screening, diagnosis and treatment in unimaginable ways.

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