Artificial intelligence and its potential in oncology

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The two main branches associated with Artificial Intelligence (AI) in medicine are virtual and physical. The virtual component includes machine learning (ML) and algorithms, whereas physical AI includes medical devices and robots for delivering care. AI is used successfully in tumour segmentation, histopathological diagnosis, tracking tumour development, and prognosis prediction. CURATE.AI, developed at the National University of Singapore, is a platform that automatically decides the optimum dose of drugs for a durable response, allowing the patient to resume a completely normal life. With the involvement of technology multinationals, such as Google and Microsoft, in AI and healthcare in association with leading healthcare companies, the future of AI in healthcare looks very promising.

Introduction

Humans are differentiated from other species by, among other things, their 'intelligence'. AI is generally defined as computational modelling of human behaviour or that of human thoughts. The exact meaning of AI is much debated. It is widely accepted that the concept of AI evolved closely with the development of computers that have the potential and ability to be able to have a thought process similar to humans, which includes learning, reasoning, and self-correction.

Foundation of artificial intelligence

The existence of localised patches in the brain that are responsible for specific cognitive functions was established in a 1861 study by Paul Broca (1824–1880) on aphasia (speech deficit) in patients with brain-damage. He showed that the left hemispheric portion of the brain has localised speech production, and this is now known as Broca's area. In 1873, Camillo Golgi (1843–1926) developed a staining technique that allowed the observation of neurons in the brain. Santiago Ramón y Cajal (1852–1934) later used this technique for his revolutionary work on neuronal structures of the brain. It was not until the 1930s that mathematical models were used by Nicolas Rashevsky to study the nervous system.

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Therefore, AI evolved from the research efforts of scientists from a variety of disciplines, including mathematics, philosophy, economics, and neurosciences [1]. Table 1 highlights the history of programming and AI.

Artificial intelligence and medicine

There are two main branches of AI in medicine: virtual and physical.

AI in medicine: the virtual branch

The virtual branch of AI in medicine mainly comprises ML, which involves mathematical algorithms that help in improving learning through experience. There are three main types of ML algorithm: (i) unsupervised (finding patterns); (ii) supervised (classifying and predicting algorithms based on past learning); and (iii) reinforcement learning (using rewards and punishments for forming a strategy to operate in a designed problem space).

Unsupervised learning involves a system looking for patterns in the unlabelled input data and further classifying the input data depending on these patterns identified. In supervised learning, MI provides the system with labelled data, which helps the system categorise the various inputs depending on what has been learnt with the labelled data. Deep learning (convoluted neural networks; CNNs) is the most common form of supervised learning.

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TABLE 1

History of programming and artificial intelligence[a]

Year	Event
1949	Manchester Mark 1: stored-program computer invented
1950s	In his paper 'Computing machinery and Intelligence', Alan Turing suggested a framework to build intelligent machines and methods of testing their intelligence
1955	Logic theorists: first AI program invented by Allen Newell and colleagues
1956	Dartmouth Summer Research Project on AI, organised by John McCarthy
1963	Success of subsequent AI programs, such as ELIZA by Joseph Weizenbaum, led to the Defence Advanced Research Project Agency funding AI projects at MIT
1980s	John Hopfield and David Rumelhart popularised deep-learning techniques; Edward Feigenbaum introduced expert systems, which mimicked the decision-making process of a human expert
1982	Japan heavily funded AI endeavours as part of their Fifth Generation Computer Project
1986	Navlab, the first autonomous car, was built by Carnegie Melon
1997	IBM's Deep Blue, a chess-playing computer program, defeated Gary Kasparov, a world chess champion and grand master; first publicly available speech available software developed by Dragon Systems
2000s	AI becomes an industry in its own right

[a] Based on Ref. [35].

CNNs are available in both 2D and 3D and act to extract features that are then further classified.

Supervised classification methods incorporate large amounts of prior knowledge in the form of a training data set with known tissue labels. From this training data set, the algorithm learns decision boundaries between tissue classes in high-dimensional feature space, which can then be applied to unlabelled test data. The output in supervised learning is defined. By contrast, the output is not defined in unsupervised learning. Instead, this approach works on the assumption that there might be some pattern observed in the input data that will be reflected in the output.

Reinforcement learning, in the context of AI, is dynamic programming that trains algorithms using a system of reward and punishment. A reinforcement learning algorithm, or agent, learns by interacting with its environment. The agent receives rewards by performing correctly and penalties for performing incorrectly. The agent learns without intervention from a human by maximising its reward and minimising its penalty.

Examples of supervised learning algorithms include linear and logistic regression, support vector machine, Naive Bayes, neural network, gradient boosting, classification trees, and random forest approaches. Clustering algorithms, such as K-means, hierarchical clustering, or mixture models, attempt to discriminate and separate the observations in different groups and are also unsupervised approaches.

The application of the above concepts to healthcare has led to an era of cognitive computing in which such models can ingest a large amount of data to detect patterns that they have previously been exposed to. For example, targeted therapies have been used in patients with cancer with limited success despite oncologists attempting to define subsets of patients who might benefit from a specific treatment. However, this definition is based on huge amounts of data associated with patient genomics, imaging, comorbidities, and previous treatments. ML approaches can help oncologists analyse these data during different stages of therapy, including diagnosis, treatment, follow-up, and prognosis. AI can handle and classify enormous amounts of data, using them to predict patterns that, when applied to therapeutics, can make the process of identifying patient groups quicker, easier, and more accurate. Thus, when combined with human expertise and knowledge, AI can significantly improve cancer diagnosis and patient care [2,3].

Artificial intelligence in medicine: the physical branch

The physical branch of AI in medicine encompasses medical devices and advanced, sophisticated robots responsible for care delivery ('carebots') that can even help during surgery [4,5].

Nanobots have been designed to overcome problems associated with the permeation and diffusion of the therapeutic agent at the site of application for targeted delivery. An example of such use is targeting a tumour that is deficit in vascularity but shows active proliferation.

The marine bacterium *Magnetococcus marinus* has the ability to transport molecules to oxygen-deficient areas and is being studied extensively for use against tumours in anoxic regions. An external magnetic source provides the initial guidance needed, after which the inherent properties of the nanobots are used to deliver the drug. This delivery is generally carried out by covalently binding the drug to nanoliposomes. Significant increases in the amount of desired drug have been reported in oxygen-deficient tissues using such an approach [6].

Regardless of their promise as healthcare applications, most AI applications in healthcare need further research, especially when it comes to human–computer interactions. Examples of systems that have been used successfully in medical diagnoses include the rule-based supervised fuzzy systems and supervised learning algorithms such as neural networks and support vector machines.

Here, we focus on the application of ML in oncology.

Machine learning and its potential in oncology

Cancer is a major cause of deaths worldwide along with metabolic disorders and infectious diseases. Factors that predispose an individual to cancer are genetic composition, environmental factors, ageing, and lifestyle. The characteristic features of tumour cells include irregular and nonregulated proliferation, adhesion, resistance to apoptosis and anticancer drugs, and senescence. Certain cancers, such as pancreatic and gastric cancers, are detected only

after they have reached their advanced stages with frequent relapses. Thus, there has been a need to shift to a more dynamic diagnostic approach that is unique to each patient, paving the way to personalised medicine in oncology for better treatment efficacy.

Bioinformatics, deep data mining, and AI are used for the identification of novel diagnostic markers, and for cancer prognosis and treatment to allow for the precise diagnosis and classification of cancer. Here, we discuss how AI has helped in cancer diagnosis and treatment, tumour segmentation, histopathological cancer diagnosis, tracking tumour development, and prognosis.

Diagnosis and treatment of cancer

Detection of cancer has become easier because of the use of ML and deep data mining. Researchers from Oregon State University successfully used deep learning to extract information from gene expression data that, in turn, helped them to classify different types of breast cancer cells. The authors were able to extract genes from the data that were useful for cancer prediction and also as cancer biomarkers and breast cancer detection. In an attempt to use AI for the classification of skin cancer, Esteva *et al*. used CNNs to classify tumours in an automated manner. They successfully demonstrated how classification of tumours is possible based on generated images because of the variability in the appearance of skin lesions. Skin cancers are usually detected using clinical screening and dermascopic analysis, followed by biopsies and histopathological analysis. By contrast, using pixels and disease labels as inputs, CNNs are able to successfully identify and classify cancers in a much less time-consuming approach [7–13]. However, CNNs have to be trained to ensure precise classification. In their study, Esteva *et al*. used 129 450 clinical images to train the CNN. Post training, the performance of the CNN was compared against the performance of dermatologists using biopsy-proven clinical images with two major classifications: keratinocyte carcinomas versus benign seborrhoeic keratoses; and malignant melanomas versus benign nevi. These classifications were selected because the former represents one of the most common cancers, whereas the latter represents one of the most deadly forms of cancer. The performance of the CNN was comparable to that of the dermatologists, which highlights the promise of this approach as a way to classify types of skin cancer. The authors also projected that the use of deep neural networks (DNNs) on mobile devices could expect almost 6.3 billion subscriptions by the end of 2021, which would extend the reach of dermatologists at a low cost to provide universal diagnostic care [14].

Tumour segmentation

Once a cancer has been diagnosed, the analysis of tumour volume is crucial for deciding the treatment protocol. Tumour segmentation, similar to tumour diagnosis, was traditionally time-consuming. The most commonly used method for the linear measurement of tumour size by radiologists is Response evaluation criteria in solid tumours (RECIST). However, the accuracy of the tumour size measurements obtained by this method can be off by almost 50%. Semiautomatic methods of segmentation, such as live wire and region growth, are often associated with significant inter- and intraobserver variation. By learning the representative complex features from the data available, CNNs make the process of tumour segmentation much simpler and more accurate. Isin *et al*. used CNNs for the segmentation of brain tumours. The inputs for the CNN were patches that were extracted from images to form a hierarchy of complex features using trained networks. Thus, brain tumour segmentation using CNN has focused mainly on network architecture design instead of on image processing [15]. Vivanti *et al*. demonstrated the use of CNNs for the segmentation of liver tumours in follow-up CT studies. The inputs required by the CNN were a baseline CT scan, delineation of the CT scan and a follow-up scan. Segmentations done in 21 tumours from 16 patients were confirmed by a radiologist and showed an average overlap error of 16.26% [16]. Weizmen *et al*. used a similar method for tumour segmentation for optic path gliomas [17]. A major advantage of CNNs over semiautomatic methods is that the need to customize handcrafted features is obviated because of their ability to automatically identify features.

Histopathological cancer diagnosis

Histomorphology has been revolutionised by precision histology, a form of deep learning. Pathology and diagnostic medicine previously depended on accurate interpretation of haematoxylin and eosin (H&E)-stained slides. Visual interpretation of the histomorphology is slow and unreliable because it is often irreproducible. However, with advances in AI, DNNs have been used to form and implement complex, multiparametric decision algorithms [16–22]. DNNs have also been used for image analysis of skin lesions with an accuracy similar to that of practising dermatologists [23]. it is likely that DNNs will soon be capable of more accurate analyses based on H&E slides owing to the developments in high-throughput whole-slide scanning technologies This will also lead to the development of a new biological data pool,which will further aid precision oncology [24–27].

DNNs act by deconstructing the images into pixels and further aggregating them sequentially to form shapes and other reproducible characteristics that can represent a diagnostic pattern. With further training images, they can be made capable of extracting even the most subtle of featural differences in clinically significant cases to aid in future classification of cancer cases. Such a data pool, which is also publicly available, is vital for training DNNs and also incorporates a follow up-study in the algorithm. Thus, machine-driven decisions will improve and optimise approaches in immunohistochemistry, which will provide more rapid and cost-effective diagnoses [28,29].

Khosravi *et al*. established the superiority of CNNs in discriminating various cancer types, subtypes, and their relative staining markers and scores Their study involved the application of immunohistochemistry and H&E-stained images of squamous cell carcinomas and lung adenocarcinomas to investigate the performance of various classifiers. The authors showed the ability of CNNs to aid histopathological cancer diagnoses. Such methods can be complementary to other clinical evaluation methods to improve knowledge of the disease and to aid in treatment decisions [30].

Image-based analysis is a cost-effective method that also reduces the workload and eliminates the need for more confirmatory tests. Robust training of these algorithms with a large number of cases confirmed at the molecular level will further help in the identification of subtle morphological characteristics that will be able to predict more precisely the presence or absence of molecular deformities typical of cancer.

Tracking tumour development

Deep learning has also been used to track and quantify the size of the tumours during treatment for the detection of any overlooked metastases. This practise was adopted by researchers at the Fraunhofer Institute for Medical Image Computing in Germany. The deep learning algorithm becomes more accurate as the number of CT and MRI scans it reads increases (Fig. 1).

Another feature of such platforms is their use for image restriction, in which the software itself aligns images of the tumour from different clinic visits of a patient for easy comparison. Such techniques are useful to detect metastases in cancers of the bone, ribs, and spine. Currently, such metastases are usually overlooked because of time constraints in clinical practise. Google Research is also working on deep-learning tools and techniques that will be capable of naturally complementing the workflow of pathologists. Their deep-learning algorithm, Inception, has been trained using images for the identification of the spread of breast cancers to the adjoining lymph nodes. This algorithm obtained a localization score of 89%, 16% more than the accuracy rate of pathologists (73%.). This automation of tumour tracking aids improved cancer management and will highlight the need for timely interventions wherever possible [31].

Prognosis detection

Prognosis establishes the seriousness and the stage of the tumour, which reflects the survival rate of the patient. The procedure of analysing the cancer stage is crucial for prognosis, but is associated with various limitations. A prediction model was developed by Yung *et al*. using deep learning for the survival rate of patients who had undergone a gastrectomy. The deep learning-based prognosis detection had a superior prediction ability compared with predictions based on the regular Coz regression. It showed that deep learning can provide a more individualised and precise risk-based stratification [30]. In another study of cancer prognosis, Turkki *et al*. quantified tumour-infiltrating immune cells in slide analyses of breast cancer samples using an antibody supervised deep learning approach. A pretrained CNN was used to extract regions and pixels that were then compared with a classification based on texture and visual assessment by pathologists. The F score achieved by the CNN approach was higher than that of the pathologists. Thus, this study showed quantitatively how deep learning can be used to study the infiltration rate of breast cancer samples [32–34].

Concluding remarks

The inherent complexities associated with malignancies call for the use of state-of-the-art technologies and concepts in the diagnosis and treatment of cancer. The uniqueness of cancers makes the mapping of their progression and early diagnosis difficult. Deep learning has been applied successfully to areas that were previously difficult to understand and is setting new standards of cancer care. For all AI applications, training of the algorithm is vital and, thus, is the most important step in developing a deep-learning platform for cancer care. IBM Watson Oncology has raised the bar of care in cancer by providing a cognitive computing platform that helps physicians to better interpret clinical infor-

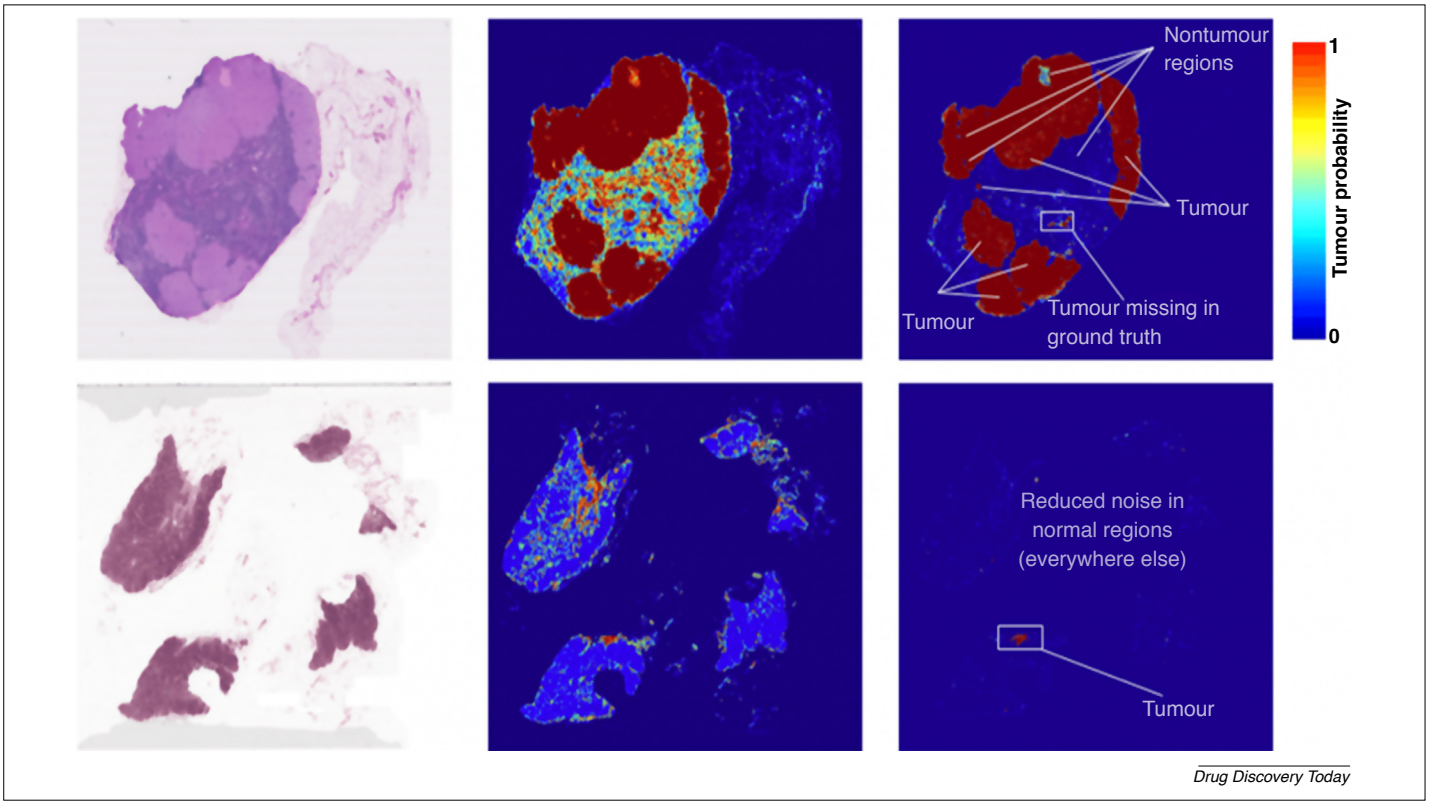

FIGURE 1

Algorithm for tracking tumour development visually (https://www.techemergence.com/deep-learning-in-oncology/). Google's deep learning tumor prediction maps that capture images throughout the course of the treatment to understand the effect of the treatment on the tumour size.

mation and identify individualised treatment plans specific to each patient. With more interest being shown in the automation of cancer care, many efforts are underway for merging cancer care with AI. The latest AI platform to be developed is CURATE.AI. This smart platform evolves with disease progression, thus enabling the optimisation of care throughout the course of treatment. It has been used successfully for patients with metastatic castration-resistant prostate cancer and is being extrapolated to other forms of cancers. Currently, NVIDIA, in association with the National Cancer Institute, US Department of Energy, and several other national laboratories, is working on an AI platform called CANDLE, which is a common discovery platform that aims to bring the power of AI to cancer treatment (https://nvidianews.nvidia.com/news/nvidia-teams-with-national-cancer-institute-u-s-department-of-energy-to-create-ai-platform-for-accelerating-cancer-research).

Therefore, AI has shown its potential to overcome many of the problems associated with the diagnosis, prognosis, progression, and treatment of a range of cancers. This transition from traditional to automated means of cancer care is promising and is likely to set new standards of cancer care to help improve patient survival rates.

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