Harnessing AI: Revolutionizing Cancer Care and Research

Maria Shuboderova[1], Darnell K. Adrian Williams[2]

[1]Palisades Charter High School, 15777 Bowdoin St, Los Angeles, CA 90272, USA.
marish051808@gmail.com
[2]Albert Einstein College of Medicine, MD-PhD Medical Scientist Training Program, 1300 Morris Park Ave, Bronx, NY 10461
darnell.williams@einsteinmed.edu

Abstract

Introduction/Background

Following heart disease, cancer is the second leading cause of death, with approximately 609,820 deaths predicted to occur in the United States in 2023. With this in mind, identifying more sophisticated and efficient methods of diagnosing cancer is crucial. This paper discusses the promising role of artificial intelligence in the field of cancer, focusing on convolutional neural networks and other deep learning models.

Methods

We conduct a literature review, in which peer-reviewed articles in BioMed Central, Pubmed, Google Scholar, Nature, Science Direct, and National Cancer Institute (NCI) databases are analyzed, focusing on publications between 2016 and 2023. Through the use of the developed inclusion and exclusion criteria, the articles utilized in this paper are narrowed down to 101 articles. Articles are only selected if published within the last seven years and contain important keywords, such as “artificial intelligence”, “cancer”, and “machine learning”.

Results

AI models have proven effective in the early diagnosis of many cancers through imaging and pathology, including lung, breast, gastric, and prostate cancer. Indeed, deep learning models such as convolutional neural networks have proven to be highly accurate in their validation test sets, in which several reached high accuracies comparable to expert physicians.

Discussion/Future Work

As cancer continues to have a grave impact on individuals worldwide, it is crucial to develop more efficient methods for cancer diagnoses. In the near future, we must work towards addressing the challenges standing in between implementing AI into clinical practice. These challenges include resolving both legal and ethical concerns, biases, availability of training datasets, and interpretability.

Conclusion

The high accuracy of several artificial intelligence models in recent studies demonstrate their potential to aid physicians. The articles selected in this review discuss the achievements, challenges, and future of such algorithms within the field of cancer.

Keywords
Cancer, Artificial intelligence, Machine learning, Deep learning, Neural Networks, Cancer imaging, Cancer pathology, Literature review, Oncology

Introduction

Cancer Rates

Following heart disease, cancer is the leading cause of death, with an estimated 609,820 cancer deaths and 1,958,310 new cancer cases predicted to occur in the United States during 2023. To put it in perspective, this estimate is equivalent to 5,370 new cancer cases arising each day (1). Moreover, statistics in 2020 indicate that cancer was the cause of approximately 17.8% of all deaths in the United States, with both cancer and heart disease accounting for half of the overall deaths reported (2). Furthermore, survival rates are highest “for cancers of the thyroid (98%), prostate (97%), testis (95%) and for melanoma (94%), and lowest for cancers of the pancreas (12%), liver and esophagus (21%)” (1).

In addition, breast cancer rates have been gradually “increasing by 0.5% each year since the mid-2000’s” (1); meanwhile lung cancer is the leading cause of all cancer deaths in 2020, with a staggering 1.8 million deaths worldwide (3). Though reported colorectal cancer (CRC) rates have been “declining by 1.4-1.5% per year since 2012”, such cases are mainly driven by reports in older age groups, whereas adults under the age of 50 have witnessed an increase of almost 2% (1). When looking ahead in time, global cancer rates are not predicted to decline if the rates reported in 2020 continue to remain constant. Unfortunately, the estimated 19.2 million new cancer cases in 2020 are expected to increase by 47% in 2040 to 28.4 million (3).

Cancer Diagnosis

Cancer goes through a prolonged, complex path from initial symptoms to cancer grading and staging. When a patient presents with a certain set of symptoms, the physician will obtain information regarding the patient's medical history and risk factors that may assist in pointing toward the risk of cancer or other diseases. These observations may result in the order of lab tests, scans, or other procedures to determine the extent of the abnormality and confirm the presence of malignancy (4). Lab tests usually involve the examination of bodily fluids, such as blood tests, urine samples, or tissue biopsies, though ordered lab tests differ for every patient based on their symptoms and history. One of the most common lab tests ordered for cancer patients is the complete blood count, which measures the number of red blood cells, white blood cells, hemoglobin, hematocrit, and platelets (5). On the other hand, imaging tests such as CT, MRI, or nuclear scans allow physicians to locate the malignancy and the best site for a potential biopsy (4).

To confirm the presence of cancer, the physician may order a biopsy, in which the most accessible abnormal area is extracted as a sample and sent to a pathologist. Under a microscopic slide, the pathologist can stage, grade, and provide the diagnostic details. Tumor grading describes the tumor's microscopic appearance, in which tumors have normal-appearing cells and are thus referred to as well-differentiated. On the other hand, high-grade tumors have peculiar-structured cells and are described as poorly differentiated. Poorly differentiated tumors are usually more aggressive, have a worse prognosis, and tend to grow and spread at a faster rate (4, 6).

On the other hand, staging describes the tumor's gross appearance, such as its invasion, tumor size, and anatomic extent. The TNM system is a classification system of three categories for carcinoma and helps define the overall stage of the tumor. The T category refers to the size and spread of the primary tumor, the N category determines the potential extent of cancer spread in the regional lymph nodes, and the M category determines the distant metastasis, or whether the cancer is present in distant areas throughout the body. The TNM system allows cancer to be categorized into stages I-IV, in which stage IV is the most extreme. Moreover, staging is a crucial prerequisite in determining the most appropriate treatment (6, 7).

That said, detecting malignancies is a difficult task in which various characteristics may contribute to diagnostic errors so much so that a staggering 15% account for error rates in cancer tissue diagnosis (8). Several factors that may contribute to the challenges faced in diagnosing cancers include dense tissues masking underlying lesions in mammograms, suboptimal image quality, or inaccurate interpretations of subtle imaging patterns (9). That said, artificial intelligence (AI) has proven to be an assistant to physicians in the field of oncology, allowing for more specific and quick identifications of malignancy. With this in mind, integrating AI into the oncological workplace will assist physicians with more speedy diagnoses and fewer inaccurate results, thus helping reduce the high physician burnout rates observed thus far. Subsequently, such results will benefit patients due to the reduction of time in determining a diagnosis and fewer diagnostic errors, thus reducing medical costs.

As a result of difficulties in diagnosis and with cancer being a prevalent cause of death and plaguing millions of individuals worldwide, the pressure experienced by physicians in oncology is frequent. Shanafelt et al. reported an average of 57.6 hours devoted to professional activities and the treatment of 52 outpatients per week when surveying 1490 oncologists in the US (10). In another study, Banerjee et al. collected 595 surveys from 40 European countries to measure burnout in the oncological field for professionals under 40 years of age. Out of all the participants, 71% were burnt out, with characteristics relating to emotional exhaustion, feelings of cynicism, and a loss of purpose and meaning in work becoming significantly related to an unstable work/life balance (11).

AI-assisted diagnoses have been shown to save time for physicians and allow for more accurate diagnoses, as seen through their high area under the receiving operating characteristic (ROC) curves (AUCs). ROC curves, visualized by a graph, demonstrate "the performance of a binary diagnostic classification method", by connecting coordinates through the x-axis, indicating the specificity, and the y-axis, representing the sensitivity obtained from the test result. Sensitivity refers to the amount of individuals who have a certain disease and are tested positive, while specificity indicates the amount of individuals who do not have said disease and are tested negative. On the other hand, the AUC of a system measures its accuracy based on the closeness of the ROC curve to the upper left corner of the graph (12).

The potential of AI assisting in quick malignancy detection was demonstrated by Zhao et al., who trained, validated, and tested an AI model based on a deep neural network (DNN) with 12,222 cases of 99mTc-MDP bone scintigraphy (BS) images. Its ability to detect bone metastasis was evaluated in a competition with three nuclear physicians with at least five years of experience with a new dataset. The AI model, with an AUC of 0.955 for prostate cancer, 0.988 for breast cancer, 0.957 for lung cancer, and 0.971 for other cancers, required 11.3 seconds to evaluate 400 cases. On the other hand, it took 116, 140, and 153 minutes, respectively, for the three physicians to interpret the same dataset with an accuracy of 89.00%, thus allowing AI to save up to 98.99% of time dedicated to the interpretation of images. Moreover, the model demonstrated a remarkable capability in the recognition of small lesions and an overall accuracy of 93.5% (13). It is important to note, however, that the potential of AI continues to have several limiting factors, and the jobs of physicians are more complex.

Artificial Intelligence

"Artificial Intelligence" was first termed by John McCarthy et al. in a proposal for the Dartmouth Summer Research Project in 1956 (14). Before John McCarthy, however, Claude E. Shannon was one of the first to propose the implementation of a computer in chess in 1945. Additionally, Shannon listed several other uses of such computers in a similar direction, such as orchestrating a melody, adapting capabilities of logical deduction, and constructing strategic decisions in simplified military operations (15). Over the next 50 years, discoveries of AI's capabilities have grown exponentially and have led to a series of advancements, of which the most noteworthy one has been chess.

The involvement of AI in chess was the first time its remarkable characteristics became known to the general public, with the most notable one being Stockfish, developed by Tord Romstad, Marco Costalba, and Joona Kiiski in 2008. Moreover, it has been marked as one of the strongest CPU chess engines of its time and won numerous competitions surrounding similar chess engines (16). Along with chess, AI's popularity in other fields grew exponentially, a trend that continues to this day (17).

Simply put, AI utilizes computational methods to mimic human intelligence. Machine Learning (ML) algorithms fall into the subset of AI and are divided into three main classes: supervised, unsupervised, and reinforcement learning (18,19). Figure 1, initially found in Chiu et al.'s article, illustrates such types of ML algorithms (20). Supervised learning algorithms require annotated, labeled datasets with inputs and desired outputs. When encountered with new datasets, the algorithm utilizes previously learned information from its labeled training dataset to notice familiar patterns (20). Unsupervised learning, however, does not require annotated datasets and can be trained with unlabeled data, allowing the model to independently separate the data into clusters and associations (18). Though more accurate than unsupervised learning algorithms, annotating datasets for training supervised learning models is time-consuming and labor-intensive. An approach to combine the advantageous sides of the two algorithms results in semi-supervised learning (20).

Several hybrid approaches, such as transfer learning, are employed to compensate for a challenge encountered when training algorithms. Transfer learning involves utilizing learned parameters from pre-trained models to perform another task, saving computational costs and reducing the requirement for training datasets (21). Lastly, reinforcement learning is a framework trained through trial-and-error, as it interacts with its environment or dataset and learns through reward functions or penalties (18,19,20).

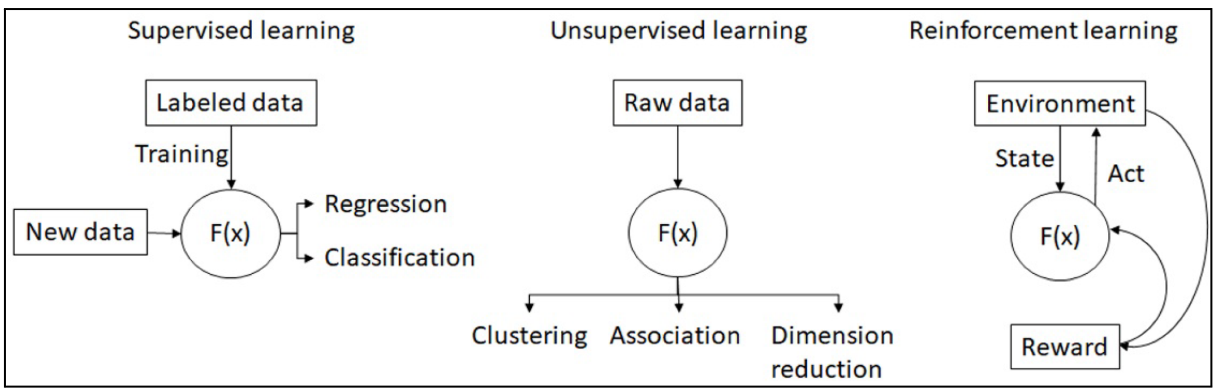

Figure 1: The three types of learning methods commonly used in ML algorithms; supervised learning, unsupervised learning, and reinforcement learning. Though different algorithms are able to combine the best of the ML models into one, such as semi-supervised learning, the three presented above indicate the most general categories used. The following figure comes from the open-access 2022 article by Chiu et al. (20), distributed under the Creative Commons Attribution license (https://creativecommons.org/licenses/by/4.0/).

Artificial Neural Networks (ANNs) fall into the subset of ML, utilizing complex computational layers to mimic connections occurring between neurons in the human brain. ANNs travel in one direction, starting with an input layer, which acts as a receiver of information, a hidden layer that reiterates the information, and an output layer that provides the prediction (22). ANNs consist of millions of “neurons” separated into successive layers. Within each layer, every neuron is interconnected to all the neurons in the layer above and below it, through which it can receive and send information down the succeeding layers until it reaches the final output layer (23).

Deep Learning (DL) is an extension of ANNs that contains several hidden layers and generally requires vast volumes of training data, which may become a limiting factor. That said, DL algorithms are known for making inferences and identifying complex patterns that would otherwise be too complicated for typical ML algorithms (24). Within DL algorithms fall in convolutional neural networks (CNNs), which are more complex networks specializing in image-based datasets. All in all, AI encompasses various, complex subsets with unique functions, as demonstrated in Figure 2, initially found in Gastounioti et al.'s 2022 article (25).

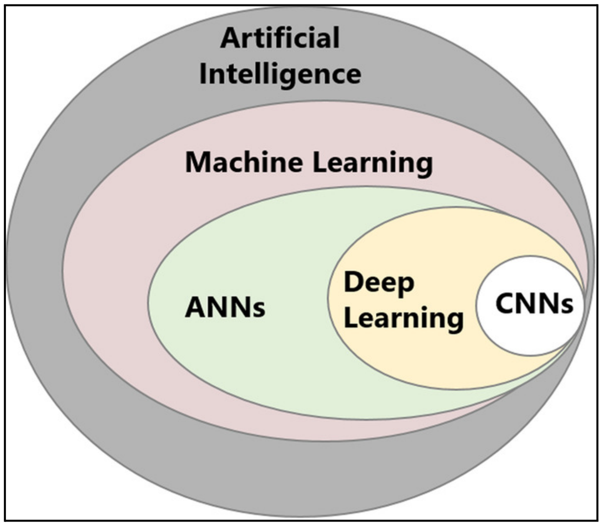

Figure 2: Different types of algorithms within the umbrella term of AI. The following figure comes from the open-access 2022 article by Gastounioti et al. (25), distributed under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

In recent years, AI has taken significant steps in entering the field of medicine, especially in the field of oncology, where it has proven its capabilities in the diagnosis and detection of malignancies. One of the most notable advances of AI in cancer was the Cancer Metastases in Lymph Nodes Challenge 2016 (CAMELYON16) conducted by Ehteshami Bejnordi et al., where 32 algorithms were developed and further assessed on their ability to detect metastasis in axillary lymph node slides. Furthermore, the study included 11 pathologists who interpreted 129 images under a simulation exercise with a time constraint designed to mimic pathological workflow. In contrast to the top-performing algorithm that achieved an AUC of 0.994, the 11 pathologists had a mean AUC of 0.810. Moreover, the 10 top-performing algorithms achieved a higher mean AUC of 0.885 in detecting micrometastases, while the highest-performing pathologist scored an AUC of 0.808 (26).

As cancer cases and deaths continue to be present globally, the necessity for more sophisticated and efficient methods of assisting physicians in oncology continues. The capabilities of AI algorithms may benefit physicians and patients alike, assisting in the detection and diagnosis of malignancies that may have been otherwise unnoticed. This review discusses the effectiveness of AI in cancer, major studies contributing to these advancements, its challenges, and the future it could hold in the field of oncology.

Methods

The objective of the review is to examine the current state-of-the-art of AI in the field of cancer and analyze the challenges it faces in its respective fields. Hence, a literature review is conducted with the aim of finding recent articles on the topic of interest.

Sources

The databases utilized to search for articles are credible, peer-reviewed, scholarly sources. Such articles are extracted from the BioMed Central, Pubmed, Google Scholar, Nature, Science Direct, and National Cancer Institute (NCI) databases for studies concerning the integration of AI in the field of oncology, with the review concluding on August 28, 2023. Utilizing keywords pertaining to the purpose of the literature review allows for a more effective search of studies relevant to the subject at hand. Such keywords include “artificial intelligence”, “deep learning”, “machine learning”, “convolutional neural network”, “cancer”, “diagnosis”, “oncology”, “neural network”, “ pathology”, and “cancer imaging”.

Inclusion and Exclusion Criteria

The developed inclusion criteria consists of articles written in English, published from 2016 to the present day, relating to cancers and AI, coming from a credible source, and peer-reviewed. On the other hand, articles containing no relation to both cancer and AI, not written in English, published before 2016, not peer-reviewed, and do not come from a credible source belong to the exclusion criteria. Moreover, articles involving non-malignant diseases are excluded. Through the following keywords, as well as the articles fitting into the inclusion criteria, 101 articles were extracted and further utilized in this review. Of these, the role of AI is tested for the purpose of several clinical procedures and different types of cancers in mind, such as breast, gastric, or lung cancer. Moreover, a majority of papers included consist of clinical trials and reviews.

Results

AI algorithms within cancer have been utilized, researched, and improved to aid physicians and patients alike. Advances towards its implementation into the oncological setting have been in the works since 2018 when the Food and Drug Administration (FDA) began approving AI medical algorithms in cancer care with a fast-track approval plan (27). Though utilized in assisting physicians with many tasks in the process of diagnosing cancer, a 2022 study by Luchini et al. indicates that 54.9% out of 71 FDA-approved AI-based devices account for cancer radiology, followed by “pathology (19.7%), radiation oncology (8.5%), gastroenterology (8.5%), clinical oncology (7.0%) and gynecology 1 (1.4%)” (28). With its rising development in this field, physicians have high hopes for its capabilities and its subsequent, hopefully positive, effects on performance, especially for physicians with less expertise (29). Most notably, however, AI has been praised for its ability to learn and analyze images at a faster pace and thus saving time for physicians. For instance, Zhao et al. demonstrated how the use of a DNN trained on BS images with an accuracy of 93.38% was able to decrease image interpretation time by 99.88% when compared to three nuclear physicians (13). In another study led by Wu et al., the developed Cystoscopy Artificial Intelligence Diagnostic System, or CAIDS for short, utilized 69,204 cystoscopic images from six hospitals for its training, internal validation, and external validation datasets. With an accuracy of 0.977 and a sensitivity, specificity, and negative predictive value exceeding 0.975, CAIDS required 12 seconds to evaluate 260 images. In contrast, the shortest time, which was achieved by an expert urologist, was 35 minutes (30).

In most clinical trials, ML algorithms are developed using training datasets extracted from public or private datasets, refined through validation datasets, and further evaluated through a test set (31). It is critical to note the difference between internal and external tests in determining an algorithm's performance and accuracy. Essentially, internal tests are conducted by the developers of the AI, while external tests are conducted by a separate, independent institution. To reduce bias, however, a majority of algorithms are tested using datasets from different institutions, thus producing accurate results rather than overestimating their capabilities (32, 33).

Within oncology, AI has not only been evaluated on its performance in detecting, diagnosing, and classifying cancer but has also been utilized in identifying precancerous areas. This ability was tested within cervical cancer in a 2019 study covered by the NCI, where the developed algorithm was able to identify precancer from images of a cervix at an AUC of 0.91, exceeding that of a human expert review, which achieved a score of 0.69 (34).

With multiple algorithms accessible for use, a question regarding which is the most efficient and accurate arises. Nonetheless, such inquiry must take into account the specific cancer type to which the algorithm is being applied. When developing an AI algorithm for the early detection of thyroid cancer, for instance, Olatunji et al. evaluated the performances of support vector machine (SVM), random forest (RF), ANN, and Naïve Bayes (NB) techniques. Out of the four AI architectures, RF achieved the highest accuracy of 90.91%, followed by the ANN (88.64%), SVM (84.09%), and finally NB (81.82%) (35). In another study evaluating the performance of five ML algorithms (XGBoost, RF, SVM, NB, and logistic regression) for the diagnosis of ovarian cancers, Akazawa and Hashimoto discovered that XGBoost and RF held the highest accuracies, with AUCs of 0.80 and 0.78, respectively (36).

Convolutional Neural Networks (CNNs)

Several fields within oncology began adopting new technology within their respective workplace, the most notable being whole slide images (WSIs), which provide high-resolution digital images and easier methods of obtaining diagnostic results. Nonetheless, WSI brings about a subsequent issue of being too tedious to fully visually analyze (37, 38). Thus the use of AI comes into play, and although ML methods are being utilized in this practice, CNNs have led the way in the integration of AI in cancer.

Through layers of convoluted filters, such architectures can detect relevant image features similarly to a human brain and deliver an output of “one or more probabilities or class labels” (39). In other words, a primary reason for the popularity of CNNs in this field is due to their efficiency in learning directly from images, and though they require more computing power, they can derive imaging patterns from the provided data (31). With this in mind, the overall use of CNNs in WSIs has become an increased focus in recent studies, as it allows for a simpler method of diagnosis for pathologists as well (40). The potential of such algorithms has been highlighted in several cases, where utilizing them allowed for accurate results, saved more time during training, required little to no annotations, and was more efficient. In a January 2022 competition involving Bulten et al., "1,010 teams consisting of 1,290 developers from 65 countries" participated in the Prostate Cancer Grade Assessment (PANDA) challenge, in which the participants submitted at least one algorithm trained on the same 10,616 biopsy images. Within the winning and top-scoring teams, a common characteristic observed was that developers chose extracted patches of images from the WSI provided and fed them into a CNN (41).

CNNs have been popularized for being "complex mathematical algorithms" and have been applied in, but not limited to, histopathology, radiology, and endoscopies (42). Moreover, such neural networks have been trained for numerous objectives within cancer to assist oncologists in a myriad of cancer types. A study by Xu et al. demonstrated the nature of such algorithms, in which a CNN architecture was trained and tested with 1260 2D images extracted from 63 optical tomographic images to diagnose breast cancer. The algorithm yielded a high performance within its test set, with a 90.2% accuracy rate, 0.80 specificity, and 0.95 sensitivity (43). Through a training data set of 5403 esophagogastroduodenoscopy (EGD) images indicating pharyngeal cancer, Tamashiro et al. developed a deep convolutional neural network (DCNN) architecture capable of identifying 40 out of 40 lesions in 28 seconds during its validation set of 1912 images. In addition, the model was able to identify three lesions under 10mm in size (44).

Nonetheless, AI-based systems present drawbacks in which certain characteristics, invasion type, and image quality cause false positive and negative interpretations. For instance, Horie et al. trained a CNN with 8428 images from 384 patients on esophageal lesions confirmed to be esophageal squamous cell carcinoma (ESCC) or adenocarcinoma. After its training, the CNN took 27 seconds to analyze, interpret, and distinguish between advanced and superficial cancer from an independent testing dataset of 1118 images. Overall, it achieved an accuracy of 99% and 92% in differentiating between superficial and advanced cancers, respectively. Of all the false positives interpreted by the algorithm, 50% accounted for shadows within the images, whereas half of the false-negative images were caused by difficult conditions (45). Sandback et al. constructed a CNN algorithm based on hematoxylin and eosin (H&E), or stains used to view tissue slides at the cellular level, WSIs for "tissue detection, classification, and slide-level analysis" from breast cancer biopsies. In the internal testing dataset of 2252 slides obtained from 1090 patients, the algorithm achieved an AUC of 0.998, with 98.27% specificity and 99.02% sensitivity. Whereas in an external validation test set of 841 H&E slides, the CNN had an AUC of 0.990, a 93.57% specificity, and 95.51% sensitivity (46).

That said, deep learning models require vast quantities of computational power, in which manually annotating data, such as CT scans, is laborious and time-consuming (24). Thus, rather than utilizing public or private datasets alone for training and establishing parameters for algorithms, researchers opt for transfer learning even with CNNs. Not only does this method appeal to individuals without expertise in training algorithms from scratch, but it also combats the long-standing concern of DL algorithms requiring extensive training data (21, 47). For instance, Hiroya Ueyama et al. programmed a CNN computer-aided diagnosis system from ResNet-50, a 50-layered CNN architecture previously trained from an ImageNet database of over 14 million images. After being further trained on 5574 ME-NBI images and evaluated with a testing dataset consisting of 2300 images, the CNN achieved a staggering AUC of 0.99 with a 98.7% accuracy (48). In another study, Esteva et al. utilized transfer learning on a pre-trained GoogleNet Inception v3 CNN architecture and further trained it with their own developed dataset of 127,463 dermatologist-labeled biopsy images for image-based diagnostic tasks for skin cancer. When compared to 21 board-certified dermatologists, the algorithm matched their performance in "keratinocyte carcinoma classification, melanoma classification and melanoma classification using dermoscopy" (49). Likewise, Tandel et al. demonstrated the high performance of transfer learning on CNN-based systems, where such an algorithm outperformed 6 different ML approaches in a 2020 study regarding brain tumor classifications (50).

With several approaches to developing an AI algorithm, one may question which method is most efficient, requires the least computational power, and produces the most accurate results. A trial by Zhu et al. explored this concern, utilizing three distinct computational methods for testing CNN architectures for identifying and differentiating breast cancer molecular subtypes from dynamic contrast-enhanced magnetic resonance imaging. Three computational methods for training the CNN included learning from scratch, transfer learning, and deep feature extraction, in which a distinct network acts as an extractor of distinct features received from the dataset. Out of the three, the learning method for reaching the highest AUC was the off-the-shelf deep feature approach, with its highest score being 0.65, followed by transfer learning, with the best performance standing at 0.60, and finally training from scratch, where its best performance demonstrated a score of 0.58 (51).

Another type of neural network famously known for its processing and prediction of sequential data is a recurrent neural network (RNN). A factor setting this algorithm apart from its other ANN counterparts is its ability to analyze data over different time points by storing previously obtained inputs and further learning from earlier steps (37, 17). Such networks have been utilized in predicting lung carcinoma subtypes by Kanavati et al., in which a DL-based model composed of an RNN and a CNN analyzed small transbronchial lung biopsy (TBLB) H&E slides. Through a training set of 579 WSIs, the RNN and CNN architecture achieved an overall AUC score of 0.993 (38).

Lung Cancer

In lung cancer, where image-based data dominates a majority of diseases analyzed by physicians, a secondary, accurate assistant becomes a necessity (20). Thus, AI algorithms have been widely employed in lung cancer, where previously established architectures such as Google's inception v3 were utilized in differentiating normal or tumorous tissues from histopathology slides at high accuracies (AUC of 0.99) (52). Moreover, ML architectures have proven to be a useful second opinion, as demonstrated by a study reviewed by the NCI, which trained an algorithm using over 1600 histopathology lung cancer slides found on The Cancer Genome Atlas (TCGA). Overall, the program was able to classify 45/54 images misclassified by the three pathologists involved in the study and differentiate normal lung tissue from the two most common forms of lung cancer: adenocarcinomas and squamous cell carcinomas (53).

Through the extraction of 1373 annotated cross-sectional lung CT images for training and validation, Coudray et al. developed a CNN and evaluated it in a test with three board-certified radiologists. When measuring the same test set of 244 CT images as one of the human radiologists, the algorithm attained an Intraclass Correlation Coefficient score of 0.959. That said, the CNN nonetheless presented a drawback, as it overestimated the lesion size by 2.97% in comparison to the radiologists, with the presence of a certain cancer invasion type being the most responsible for under and overestimations (54). Due to the complexities of the subtypes falling into the umbrella of lung cancers, different characteristics may require different treatment routes. For instance, squamous and non-squamous non-small cell lung cancer (NSCLC) requires altering treatments, thus creating a necessity for proper classifications. With the use of the Inception v3 architecture, Le Page et al. utilized a training dataset of 132 histopathological HES slides with an equal number of images representing squamous and non-squamous NSCLC lesions. In the training, validation, and test evaluations, the Inception v3 architecture received AUC scores of 0.99, 0.87, and 0.85, respectively (55).

Though the capabilities and performance of DLs go beyond those of their ML counterparts, they nonetheless introduce a limiting factor, where vast amounts of usually annotated data are required (56). Hence in several cases, researchers opted out of using mass, manually annotated datasets. For instance, an early 2022 study by Xie et al. trained a weakly supervised deep learning model based on lung cytological whole-slide images for assisting cytopathologists in differentiating between malignant and benign cases. Thus, the weakly supervised DL algorithm combatted the labor-intensive work of image annotations found in typical supervised DL algorithms and only required labels for the training and validation datasets (57).

Prostate cancer

With prostate adenocarcinoma being the most prevalent cancer seen in men, utilizing AI as a tool will assist physicians in a timely, more accurate diagnosis. Pantanowitz et al. developed an algorithm based on multilayered CNNs for image classification and tasks in analyzing WSIs of core needle biopsies (CNBs). After being trained on 1,357,480 labeled image patches, the internal test indicated an AUC for cancer detection of 0.997 and a score of 0.991 on an external validation test conducted at the University of Pittsburgh Medical Center (UPMC) (58).

One of the most widespread machine-learning algorithms developed for detecting prostatic adenocarcinoma is Paige Prostate Alpha, which categorizes the inputted whole slide image as “suspicious” or “not suspicious” from detected lesions (59). Raciti et al. evaluated the performance of Paige Prostate Alpha in the clinical setting with three board-certified pathologists when analyzing CNBs. Overall, pathologists achieved a faster performance with the algorithm than without, decreasing the time spent on each cancerous WSI slide by 13 seconds and increasing sensitivity from 74% ± 11% to 90% ± 4%. Additionally, the average sensitivity of smaller cancerous areas under 0.6 substantially increased from 46% to 96% when using Paige Prostate Alpha (60).

Gastric Cancer

Within gastric cancer, AI has proven to be advantageous in exceeding diagnostic time as well as assisting oncologists in noticing areas of malignancies that would have otherwise been missed. For instance, EGDs, an imaging source used within the cancer type, experience a setback where detection is difficult due to the subtle differences and can be assisted through the use of CNNs (61). A 2021 study by Niikura et al. trained an AI for diagnosing gastric cancer through gastrointestinal endoscopies using a dataset extracted from 500 patients, of which 51 consisted of invasive gastric cancer and 49 early gastric cancer. In total, the white-light upper gastrointestinal endoscopy images extracted from the patients resulted in 23,892 images. When evaluated with expert endoscopists, the AI achieved a higher per-image rate of diagnosing gastric cancer by 13.0% (62). In another case, Tang et al. trained a DCNN for the purpose of detecting specifically early gastric cancer, which operated by extracting features from the image and further detecting the lesion's location. Not only did the system present high AUCs within its four validation test datasets, with the scores ranging between 0.887–0.940, it also demonstrated a high diagnostic accuracy of 95.3% compared to expert and trainee endoscopists (87.3% and 73.6%, respectively). Most notably, though, the DCCN demonstrated how the trainees' performance became comparable to that of expert endoscopists with the assistance of the algorithm (63).

The high diagnostic accuracy of AI architectures in gastric cancer, especially with non-experts, was also noted by Li et al. in 2019, who trained an Inception-v3 CNN with a dataset extracted from magnifying endoscopy with narrow band imaging (M-NBI). When testing its abilities in diagnosing early gastric cancers compared to human endoscopists, however, results indicated no significant difference in the accuracy and specificity of CNN and the expert's performance. Instead, the CNN's sensitivity was higher than that of experts, while its sensitivity, accuracy, and specificity were higher than non-experts (64). Furthermore, another study by Luo et al. involving the use of an AI diagnostic system for upper gastrointestinal cancers demonstrated a much superior performance when compared to non-expert endoscopists (65). Another alternative method to the use of CNNs within the field of gastric cancer was noted by Liu et al., in which the fusion of GoogleNet and AlexNet models allowed for a higher sensitivity and specificity of 97.60% and 99.49%, respectively (66).

All in all, such algorithms have the potential to assist physicians in the oncological setting when diagnosing gastric cancer, as demonstrated by Song et al., who applied their CNN architecture with AUCs of 0.990 and 0.996 within two test datasets in a real-world scenario. The CNN, when utilized by 12 junior pathologists with a time constraint, allowed for a higher diagnostic accuracy (67). Likewise, Jiang et al. indicated an increase in clinician performance in predicting peritoneal recurrence based on CT images with the integration of the AI model. One of the participating physicians, for instance, experienced a rise in sensitivity during the training, internal validation, and external validation cohorts from 0.692 to 0.915, 0.596 to 0.938, and 0.615 to 0.944, respectively (68). In contrast, Ikenoyama et al. demonstrated that although their developed CNN algorithm had a shorter diagnosis time (45.5 ± 1.8 seconds compared to 173.0 ± 66.0 minutes in analyzing 2940 endoscopy images) and a higher sensitivity (80% and 53.4%) compared to endoscopists, it nonetheless had a lower specificity (69).

It is evident that many studies utilize DL methods, more specifically CNNs, for evaluating the abilities of AI and what effect it may have on the performance of physicians when implemented into the field. For instance, Fan et al. constructed a Multilayer perceptron (MLP), otherwise known as an ANN, as well as Logistic Regression, K-Nearest Neighbor, Decision Tree, Random Forest, and eXtreme gradient boosting classifying models through the same testing and validation datasets. As a result, the prediction of gastric cancer performed by the ANN proved to have a higher accuracy than the five classifying models (70).

Colorectal Cancer

Along with understanding which oncological field contains most of the 71 FDA-approved AI-associated devices, Luchini et al. identified that 7.0% of them account for CRC (28). Indeed, several advances within this cancer type are in progress. For instance, a 2023 study by Buk Cardoso et al. evaluated the extent to which three ML algorithms, RF, XGBoost, and NB, were able to predict CRC patient survival “from hospital-based cancer registry data in low and middle-income countries”. Achieving an AUC score of 0.882 in training and 0.858 in testing, the XGBoost architecture performed at the highest accuracy of 78%, followed by Random Forest and Naive Bayes (71). In addition to utilizing AI-based algorithms in predicting survival rates, the importance of detecting CRC from colonoscopy images was taken into account by Zhou et al., who utilized a staggering 464,105 colonoscopy images in training CRCNet, a DL-based architecture. To address several non-malignant diseases responsible for complicating CRC diagnosis, researchers included such diseases as their control group. Overall, CRCNet achieved high performance in test datasets from Tianjin Cancer Hospital, Tianjin First Central Hospital, and Tianjin General Hospital, with an AUC of 0.930, 0.961, and 0.989, respectively (72). Moreover, the use of AI-based architectures in assisting physicians, especially with time, was noted by Lu et al., in which the time taken for a pathologist to detect colorectal tumor budding decreased from 13±5 seconds to 0.03±0.01 seconds with the use of the developed Faster R-CNN model (73).

Nonetheless, the involvement of AI in CRC experiences a major drawback, where a majority of training data is extracted from a singular institution, thus lacking in providing generalized results in a field of heterogeneous characteristics presented in this cancer type (74). Fortunately, this shortcoming is currently being combated through the use of multiple institutions, providing more generalized, diverse training data. One of the most notable examples of this action was conducted by Wang et al., who further trained an Inception-v3 CNN architecture with a dataset of 14,234 CRC WSIs extracted from 14 independent hospitals and sources located in China, Germany, and the US (75).

Breast Cancer

While prostate cancer accounts for the most cancer incidences in men, breast cancer, if not including skin cancer, stands as the most significant cause of cancer in women. Thus, accurate and hopefully early diagnoses are vital for decreasing mortality rates (76). Luckily, developments of AI towards this cancer type are advancing, especially in breast cancer radiology, with the hope of it potentially becoming a secondary interpreter as well as reducing the time spent analyzing the patient's images and the occurrences of false positives (77). Before its rise in use, however, computer-aided detection (CADe) algorithms, as well as computer-aided diagnosis (CADx) assisted radiologists in interpreting the patient's exams. Developed in the same manner, both CADe and CADx algorithms are taught through the features indicating what a malignant lesion looks like, and when being faced with data, use such programmed features to locate potential suspicious lesions or evaluate the extent to which a given suspicious area contains them (78). In other words, the algorithms used in the detection and diagnosis world through the use of pre-programmed features received through the programmer. Nonetheless, the rise of AI, especially DL algorithms, opens the door to cancer diagnosis and detection without the use of preprogrammed features. In cancer imaging, for instance, the CAMELYON16 competition, which was briefly discussed previously, the use of ANNs, most specifically deep CNNs, was utilized by a majority of winning teams in constructing their algorithms. Moreover, manually annotated algorithms presented a lower performance relative to their CNN counterparts (26). In general, CNNs provide the most utility within the detection and classification of breast cancer due to their abilities in feature extraction, facilitating easier views of "malignancy in breast masses" (79). Within breast cancer imaging, especially for mammograms, in which the rates of false-positive and false-negative results are substantially high, more advancements towards the improvement of AI algorithms have been proposed as well (80). For instance, Wanders et al., when combining mammographic breast density assessments with an AI cancer detection system, achieved more accurate predictions of interval cancer "after negative screening mammography" (81).

Moreover, DL-based algorithms facilitate more accurate and faster results from physicians in breast cancer, as demonstrated by recent studies. Jiang et al. compared the performance of 19 breast radiologists with ('first read') and without ('second read') the assistance of QuantX, an AI-based breast MRI diagnostics aid. Through the average AUC values developed of the 'first read' and 'second read', the use of QuantX increased the radiologists' accuracies from a score of 0.71 to 0.76 (82). In a later study conducted in 2022, Shoshan et al. trained, validated, and tested an AI model with a cohort of 9919 women, allowing for 13,306 digital breast tomosynthesis examinations. The AI, which is an ensemble of 45 DL and 5 ML classifiers, was not only found to be highly generalizable to unseen sites, but when evaluated in a stimulated workflow radiologists were able to reduce the worklist by 39.6% (83).

In another case, Lin et al. developed a FasterRCCN algorithm to detect and classify microcalcifications in breast mammography that could assist in providing an early diagnosis of breast cancer. The study utilized a training dataset of 1,964 benign and 1,970 malignant images, as well as a test set of 426 benign and 450 malignant images for the algorithm. Overall, the FasterRCNN algorithm was able to distinguish between malignant and benign breast mammography images at an AUC score of 0.8042 (84). Additionally, a recent, 2023 study conducted by Liao et al. trained and validated EDL-BC, a DCNN-based algorithm to identify early breast cancer from ultrasound images. Regarding its AUCs on its internal test and external validation datasets, the model had a score of 0.956 and 0.907, respectively. Furthermore, the study included six radiologists with over 20 years of experience to evaluate the performance of EDL-BC within the clinical workplace. Without its influence, the average AUC achieved by radiologists was 0.716, but with it, however, the score presented a substantial rise to 0.899 (85).

Discussion

Multimodal

Due to the complex steps taken in diagnosing patients with cancer, it is important to keep in mind that the use of different data modalities is a prevalent factor in the process. Thus, in utilizing multimodal learning, an algorithm is able to accept different types of data as its input and subsequently learn to combine this information, strengthening its overall accuracy as well as assisting physicians in analyzing different types of patient data (86, 87). Such data types may include a multitude of image types, images combined with text, or images integrated with genomic data (88). An advantage to these algorithms is the substitution of additional information from other data modalities if the unimodal data is, by any means, opaque or unclear (89).

Challenges

Aside from the cancer types previously included, AI was also applied to skin, bladder, head and neck cancers, as well as pancreatic ductal adenocarcinoma (90, 91, 92, 93). Essentially, the evaluation of AI in oncology is becoming increasingly frequent, especially due to its ability to ‘think’ similarly to a human brain (94). Their abilities in oncology span from detection to predicting survival rates, such as for ESCC patients (95). Moreover, neural networks have been proven to learn at a much faster rate than medical professionals, allowing for such algorithms’ capabilities to extend to being a “knowledge discovery tool” (96). Even though numerous publications are being put out on the subject of AI in clinical practice, such as breast imaging, very few are currently being implemented into clinical practice (9). Thus, it is critical to address the long-standing issues within AI to develop more accurate algorithms for assisting medical professionals.

Lack of Data

A significant challenge standing in the way of AI becoming integrated into the oncological setting, such as in precision oncology, is the insufficiency of high-quality data (97). Due to many algorithms, especially the ones falling into the subset of DL-based architectures, requiring labeled, robust datasets, the insufficiency thereof brings about subsequently poor performance. In a 2020 review that shed light on the advancements made in deep learning radiogenomics within oncological care, Trivizakis et al. noted that the limited availability of datasets was “the most pronounced limitation for deep learning radiogenomics” (98). Thus, many solutions to this shortcoming can take effect, with the most notable being the adoption of transfer learning and the inclusion of public datasets. Utilizing pre-trained models overcomes challenges concerning the need for high-quality datasets (23, 47).

With training data extracted from a single site, a risk of overfitting occurs in which the algorithm fails in being generally applicable when applied to non-training data, such as external validation cohorts. Keeping in mind the heterogeneous characteristics of cancers found within patients, it is crucial for algorithms to be trained on diverse sets of information and not confined to a singular institution (74). Moribata et al. developed a method to combat this drawback by training an automatic segmentation model for bladder cancer magnetic resonance images using multi-vendor scanners from two institutes with a large patient cohort and diverse parameters (99).

Indeed, many benefits arise with the use of public datasets, with TCGA, for instance, combating the deficiency of information through its compilations of various cancer subtypes and data types (100, 101). In addition, such databases resolve the time-consuming challenge of collecting sufficient images (102). In a 2023 study involving TCGA’s data on patient transcriptome profiles and drug treatments, Sun and Chen constructed a DL-based algorithm capable of predicting cancer patient survival. When distinguishing short-lived and long-lived patients, the algorithm achieved an accuracy of 96% (103). However, such public datasets present another pitfall in which datasets regarding certain cancers are scarce. For instance, Mahoro and Akhloufi concluded that although DL methods are promising in image analysis, several informative datasets involving breast cancer images are not annotated or publicly available (104).

Bias

Nonetheless, the call for large datasets is not the only factor that lowers the accuracy of AI. Biases within AI fall into the risk of potentially providing inaccurate results primarily due to training datasets not equally depicting the population as a whole, especially minority groups (105, 106). Thus, when applied to said underrepresented subgroups, such as ethnic minorities or young adults, algorithms fail to give an accurate outcome and may even further aggravate already existing racial disparities (107, 25).

With this in mind, a rising concern regarding the TCGA database is brought about, as a majority of its data is from individuals of European ancestry, while individuals of Asian, African, and Hispanic ancestry are underrepresented (101, 108). Such databases, though diverse in modalities, may fail to generalize towards individuals of minorities. Some solutions have been proposed to combat biases within AI, however. For instance, Bakrania et al. encouraged future studies to "explore in-depth explainability techniques" to overcome such challenges (109).

Interpretability

In recent times, DL and "relatively less complex models with more user-friendly model representations" are criticized for being a "black box" as their reasonings are viewed as opaque and impossible to interpret (97, 22, 19). Where a physician's diagnosis accounts for the most crucial factors in a patient's treatment and path toward recovery, such difficulties refrain AI from being integrated into the oncological practice. Luckily, solutions for increasing explainability have been initiated. For instance, methods such as gradient-based analysis, evaluate pixels within an image to rule out areas responsible for the generated output (109). Color mapping provides the regions utilized by the AI in creating a conclusion, while class activation maps (CAMs) emphasize the areas of the image that contributed most to the model's decision (18, 110). CAMs have been shown to be a reliable addition to DL models within oncology such as oral cancer and oral squamous cell carcinoma, where one 2021 study features their addition in classifying "suspicious" or "normal" photographed oral lesions (111).

Ethics

From an ethical standpoint, the sharing of data raises a question regarding the "expectation of confidentiality" within the doctor-patient relationship, hindering the integration of AI in the medical field (112, 113). Thus, if AI was to be implemented in the medical field, its interpretations or decisions must be further evaluated by physicians (114). As noted by Chen et al., the degree to which a physician must supervise and oversee the AI's decision-making, as well as the party responsible in the case of which the DL is incorrect must be established (27). Moreover, in a 2020 review overviewing the use of MLPs and CNNs in detecting early breast cancer, Desai and Shah observed that the reliability of ANN algorithms is questionable, as one study indicated that its accuracy in the detection and diagnosis was lower than that of radiologists (79). Consequently, the prevalence of human physicians in the oncological practice is a necessity, even with the presence of AI.

Concerns on replaceability of physicians and legal liability regarding AI

With the continuous improvements of AI in medical care, a concern regarding whether human practitioners will eventually be replaced comes to light. Nonetheless, the chances of medical professionals being replaced by such algorithms are unlikely, as many current studies indicate a common goal of developing AI to improve efficiency and reduce the time usually needed by physicians to create a diagnosis. Such goals in current studies are supported by the lack of definitive, high-level proof of efficient autonomous AI-enabled machines (115). If such trends continue in the future, physicians will not be entirely replaced by autonomously functioning algorithms, although those who utilize AI will most certainly replace those who do not (116, 117).

Current studies demonstrate the collaborative decision-making nature arising from the introduction of AI, where it provides physicians with an analysis as its output, and the individual subsequently leverages their knowledge for the conclusive decision within the diagnosis. Moreover, the physician validates the given predictions, allowing for human feedback to improve AI's ability to manage more complex cases that were not encountered in its training data (118). Thus, rather than competing, the collaboration between the two parties complements one another, where if one system fails, the other system can potentially notice the mistake (33). Figure 3, extracted from Sezgin's 2023 article, further illustrates such an idea (118).

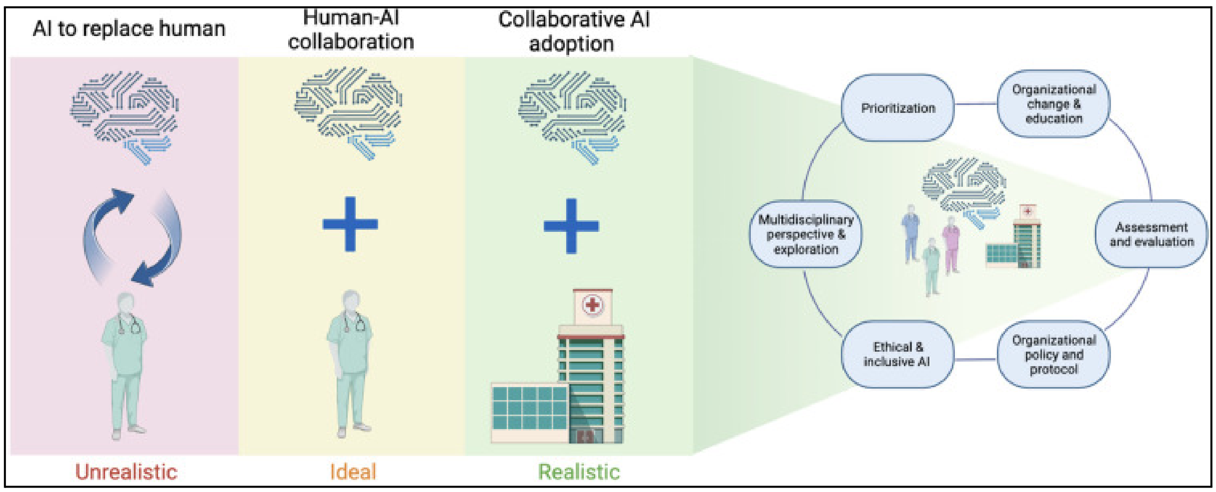

Figure 3: A summary of considerations concerning the integration of AI into clinical practice, demonstrating how the notion of AI replacing human physicians is unrealistic. Meanwhile, the partnership between the two parties is perceived as ideal. The following figure comes from the open-access 2023 article by Sezgin (118), distributed under the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/).

Although the effectiveness of AI and physicians working in tandem is positively regarded by many, a legal issue concerning liability remains. For instance, if an AI were to give a false-negative diagnosis of a breast cancer patient, who, in the given scenario, will be liable for the misdiagnosis? Would it perhaps be the mistake of the AI, or would the responsibility fall upon the physician overseeing the analysis of the algorithm? What of the hospital that signed the approval for the adoption of the AI-based model? Might the responsibility and the consequences of the misdiagnosis fall into the hands of the algorithm's developers?

The question of who is liable is rather nuanced, where, at least for the United States and Canada, there are no established legal frameworks overseeing AI in medical care. Due to the new nature of AI, there has been a finite amount of legal precedents concerning liability within this field (119). Thus, it is currently difficult to arrive at a definitive answer on the bearer of responsibility in the event of an unjust medical outcome (120). The lack of clarity on such a complex situation leaves the public opinion to speculate on the true responsibility. A 2021 survey by Khullar et al. explored this inquiry, where 1007 participants, consisting of both physicians and the general public evaluated whether the physician, the vendor or company licensing the algorithm, the healthcare organization that purchased the algorithm, or the FDA or a governmental entity approving the algorithm is liable in the case of an error. As a result, both the public and physician groups (66.0% vs 57.3%) found physicians to be most liable, with the public being more inclined to choose the physicians. Meanwhile, the physician group was more inclined to regard the company (43.8% vs 32.9%) and the healthcare organization (29.2% vs 22.6%) to be more responsible than the public (121).

To a certain extent, it may be reasonable to suggest why the responsibility for an AI's results is primarily placed on physicians, as they bring about the final judgment based on the patient's data. When examining the current state of liability revolving around medical AI models, MALIHA et al. indicate that cases hold physicians accountable for errors occurring due to AI and ML outputs (122). If the demand for liability falls on the AI's developer, or its software development company, one may argue that they stand as a third party and it is the hospital and physicians' responsibility to exercise their professional judgment rather than entirely relying on an AI. Nonetheless, Smith & Fotheringham add by noting how the clinician utilizing an algorithm that produces mostly accurate results may experience an 'atrophy of vigilance', where one's attention declines when surveilling the AI's recommendations (123).

As AI-based algorithms advance into the medical field, especially in cancer care where the early detections of malignancy are of the utmost importance, both hospitals and medical professionals must be trained on the usage of such systems, and thus have ultimate responsibility (124).

The future of AI in the field of cancer

It is without a doubt that the abilities of AI will advance exponentially and extend to more medical fields. The studies included in this literature review demonstrated the remarkable ability of AI within a multitude of cancer types and different data modalities. Thus, the upcoming years will most likely witness AI advance and become implemented in such specialties. In a recent 2023 study, Cabral et al. recorded the responses of approximately 1,000 AI and cancer researchers on a web-based survey regarding the future of AI in cancer care. Of these participants, over 73.13% predicted AI would be involved in grading and classifying cancer, and 69.08% expected it to provide more reliable diagnoses within the next 10 years. Regarding the areas of interest which will benefit from the use of AI the most, cancer radiology was chosen by one-third of the participants, followed by pathology and clinical oncology (27.02% and 20.29%, respectively) (125).

Nonetheless, its future in healthcare, especially in oncology, is dependent on whether challenges and standards in enforcing greater measures regarding its reliability must be addressed. Future studies revolving around this subject must consequently address ways to overcome current challenges if AI is to be applied in the medical field and gain the confidence of physicians and patients alike. In the upcoming years, the transition to clinical implementation of AI must remain unbiased to any given data and need to overcome the "black box" feature that remains a prominent obstacle in current studies.

More diverse datasets extracted from individuals of diverse ancestries, containing multiple data modalities and cancer subtypes are crucial in developing reliable algorithms capable of providing a definite analysis for all patients. Moreover, the legal and ethical concerns regarding the responsibility of AI need to be addressed, and, as noted by Gowda et al., "Where the law is silent, professional societies can and should step in to fill the void, thereby fostering specialty-wide uniformity alongside patient safety". For instance, measures providing training for physicians, supporting future research, and constructing AI-specific practice guidelines should be taken by The American Society of Clinical Oncology (126).

Within the next ten years, AI will, or become closer to, entering clinical practice. With the rise of such technology, it wouldn't be a surprise if more physicians become trained and informed on how to utilize such algorithms, with knowledge surrounding the use of AI becoming more desired in the medical field. As its development progresses even more, we may see a future consisting of AI-physician collaboration rather than the currently feared replacement of professionals.

Limitations

The literature review, consisting of 101 articles regarding the current state-of-the-art of AI in cancer, does come with several limitations. As discoveries within the field progress and provide new information that was not previously known, the information discussed may become less applicable.

Conclusion

AI, when applied to cancer, demonstrates an accurate, swift performance, comparing or even exceeding that of experts. Though it bears several shortcomings, it is evident that the technology will only improve over time and hopefully become fully integrated into clinical practice, where it may assist physicians and patients alike. By conducting a literature review, this paper discusses the state of the art of AI algorithms in the cancer setting as well as its challenges, achievements, and potential future.

Abbreviations

ANN- Artificial neural network
AUC- Area under the ROC curve
BS- Bone scintigraphy
CADe- computer-aided detection
CADx- computer-aided diagnosis

CAM- class activation map
CAMELYON16- Cancer Metastases in Lymph Nodes Challenge 2016
CNB- Core needle biopsy
CNN- Convolutional neural networks
CRC- Colorectal cancer
DCNN- Deep convolutional neural network
DL- Deep learning
DNN- Deep neural network
EGD- Esophagogastroduodenoscopy
ESCC- Esophageal squamous cell carcinoma
FDA- Food and Drug Administration
H&E- Hematoxylin and eosin
ML- Machine learning
MLP- Multilayer perceptron
NB- Naïve bayes
NCI- National Cancer Institute
NSCLC- Non-small cell lung cancer
RF- Random forest
RNN- Recurrent neural networks
ROC- Receiving operating characteristic
SVM- Support vector machine
TCGA- The Cancer Genome Atlas
WSI- Whole slide imaging

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