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Artificial intelligence-aided optical imaging for cancer theranostics

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ABSTRACT

The use of artificial intelligence (AI) to assist biomedical imaging have demonstrated its high accuracy and high efficiency in medical decision-making for individualized cancer medicine. In particular, optical imaging methods are able to visualize both the structural and functional information of tumors tissues with high contrast, low cost, and noninvasive property. However, no systematic work has been performed to inspect the recent advances on AI-aided optical imaging for cancer theranostics. In this review, we demonstrated how AI can guide optical imaging methods to improve the accuracy on tumor detection, automated analysis and prediction of its histopathological section, its monitoring during treatment, and its prognosis by using computer vision, deep learning and natural language processing. By contrast, the optical imaging techniques involved mainly consisted of various tomography and microscopy imaging methods such as optical endoscopy imaging, optical coherence tomography, photoacoustic imaging, diffuse optical tomography, optical microscopy imaging, Raman imaging, and fluorescent imaging. Meanwhile, existing problems, possible challenges and future prospects for AI-aided optical imaging protocol for cancer theranostics were also discussed. It is expected that the present work can open a new avenue for precision oncology by using AI and optical imaging tools.

1. Introduction

To date, cancer remains the leading cause of global mortality. For example, new cancer cases increased from 14 million in 2012 to 19.3 million in 2020 and cancer deaths also escalated from 8.2 million in 2012 to approximately 10 million in 2020 [1,2]. Therefore, it is essential to carry out the cancer early detection, accurate diagnosis and high-efficiency cancer treatment with few side effects, which can significantly improve the survival rate and life quality of cancer patients. In addition, optical imaging techniques including various microscopy and tomography imaging methods at various scale mainly consists of optical endoscopy imaging, optical coherence tomography, photoacoustic imaging, diffuse optical tomography, super-resolution microscopy imaging, Raman spectroscopy imaging, and fluorescence imaging. Interestingly, they have received extensive attentions in both preclinical and clinical studies for cancer detection and treatment. Compared with traditional imaging methods such as positron emission tomography (PET), computed tomography (CT) and magnetic resonance imaging (MRI), optical imaging has demonstrated its unbeatable advantages for cancer oncology including high sensitivity, low cost, and visualizing both structural and functional information of tumor tissues at different scales [3–6]. In addition, different optical imaging methods are based on various optical contrasts including absorption, scattering and fluences, which are related to the hallmarks of cancer. For example, fluorescence imaging relies on the emission of light following its absorption by fluorescence probes, photoacoustic imaging is based on optical absorption of biological tissues, whereas Raman and optical coherence tomography imaging depend on the scattering of light. The downside of optical imaging is its low penetration depth, which can be resolved by using endoscopy techniques. Besides, it was discovered that the penetration depth of optical imaging can be up to a few centimeters in the second near-infrared (NIR) biological window (wavelengths from 1000 to 1700 nm) because skin and blood scatter and absorb less light at long wavelengths [7–10].

In recent years, optical imaging has gradually entered into the era of computational and intelligent optical imaging from traditional imaging mode [11–15]. The imaging mode that directly captures the specimen by the camera system was gradually replaced with the indirect imaging mode that calculates and reconstructs images through the collected data. The application of AI in the field of pathological diagnosis and

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medical image recognition has attracted extensive attention in cancer diagnosis and imaging-guided treatment. For example, computer vision, as a popular AI technology, can help identify certain features in images for with high accuracy in cancer diagnosis. It can mine a large amount of pathological and genetic data by processing and cross-referencing health and medical big data such as images, pathology and genes, aiding to access the pathological sections faster, and improve the efficiency and prognosis of cancer diagnosis. In particular, recent advances in medical imaging of cancer significantly resolve the challenge from biopsy - an invasive, unrepeatable technique that usually ignore heterogeneity within cancer. AI use data characterization algorithms to convert conventional imaging information into biomarkers for disease detection. These AI approaches have been used in radiological diagnosis, bioinformatics, genome sequencing, drug development and histopathological image analysis. Interestingly, AI has exhibited a potential ability similar to medical expert for histopathological diagnosis. And AI-aided optical imaging can acquire multidimensional high temporal-spatial resolution information by calculated reconstruction mode that the traditional microscopy techniques are unable or difficult to direct access [16–18]. Among them, the DL technology represented by data-driven and the compressive sensing technology represented by physical-model-driven improved the unpredictability of the actual imaging physical process and the complexity of solving high-dimensional ill-posed inverse problems[19–25], which also opens a new door for the development of optical imaging (Fig. 1).

More specifically, AI is a branch of computer science that seeks to simulate intelligent human behavior in computers. It is defined as a programmed machine that can learn and recognize patterns and relationships between inputs and outputs and use this knowledge effectively for decision-making on brand-new input data. Machine learning (ML) and DL are the predominant methods used to actualize AI (Fig. 2). ML algorithms rely on structured data to make predictions[26], which refers to the data that is labeled, organized, and defined with specific features. ML models process the data and identify patterns that improve clinical decision making at all levels, and these models update by themselves and improve their analytical accuracy each time [27]. ML methods are further divided into supervised, unsupervised and reinforcement learning. Supervised methods use images together with ground truth labels to train classification models, including Bayesian methods, discriminant analysis, k-nearest neighbour (kNN), support vector machine (SVM), artificial neural network (ANN), random forest, AdaBoost, and fuzzy techniques. Unsupervised methods, including Gaussian mixture model (GMM), fuzzy c-means (FCM), and k-means clustering performs vessel segmentation without training labels. Reinforcement learning can learn through a system of reward and penalties and improves its algorithm over time with the help of a constant feedback loop. The cancer images are generally distinguished and detected by DL and conventional machine learning (include rule-based learning) from those of normal tissues and healthy controls.

DL is a subset of ML, refers to a technique that autonomously learns features and tasks from a training dataset. “Deep” refers to the multiple layers of algorithms that the presented data pass through during computation, and a network of interconnected algorithms is called a neural network [28]. This was inspired by the neural connectivity in the human brain, that are designed to recognize patterns in their tasks. DL uses deep neural networks (DNNs) to develop sophisticated models with multiple hidden layers to analyze various types of data and develop prediction outputs [29]. Moreover, each step in DL allows the program to continually learn and evaluate its progress in order to reach a specific outcome. Unlike MLprograms, DLprograms require multiple layers of codes and do not require the programmer to explicitly identify specific features in an image as DLprograms autonomously learn from training datasets. Therefore, a DLprogram also requires a larger training dataset and higher computational power than that required by a conventional MLprogram. There are many kinds of DLframeworks, such as autoencoder (AE), deep belief network (DBN) and convolution neural network (CNN). Among them, CNN is the most commonly used in cancer detection, followed by AE and DBN. They are either used to analyze medical

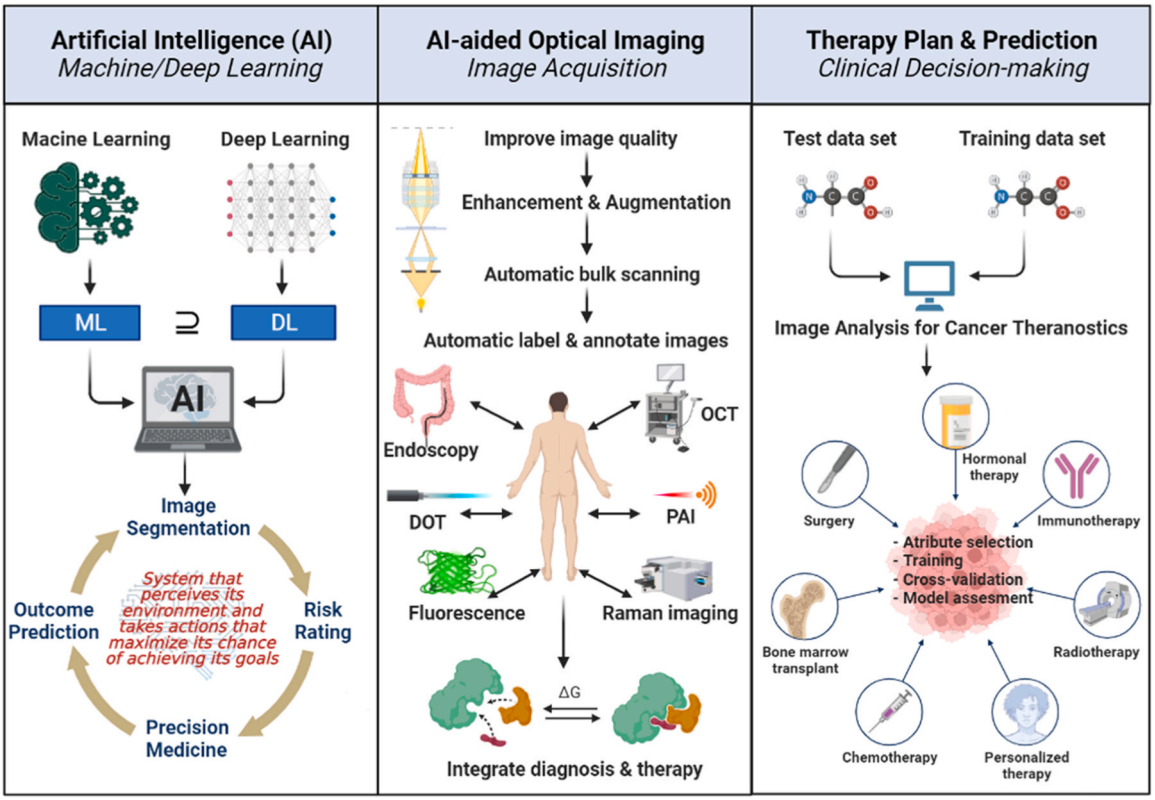

Fig. 1. Overview of artificial intelligence (AI)-aided optical imaging for precision cancer theranostics.

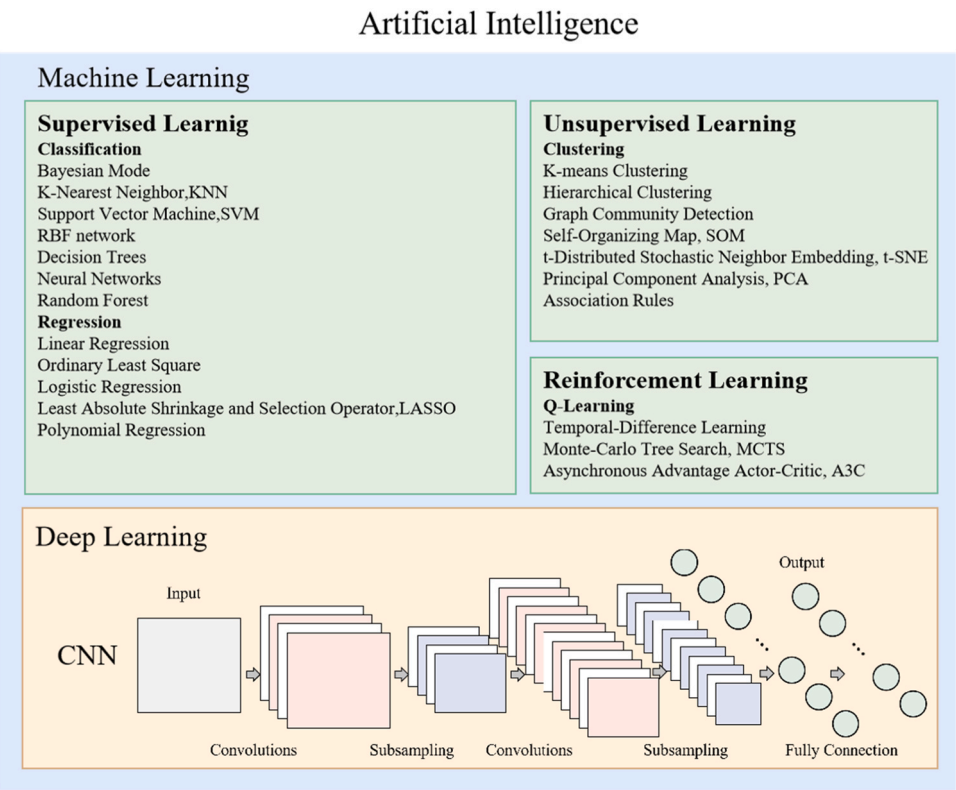

Fig. 2. The relationship between artificial intelligence, machine learning, deep learning and commonly used algorithms as examples. CNN, convolutional neural network.

images or to analyze molecular level data, such as gene mutations, gene expression data, etc. At present, DL technology cannot be applied to all types of cancer, so the existing research generally takes lung cancer, breast cancer and other common cancers as the detection target [30]. CNN is a multi-layer neural network framework, which aims to learn high-level information in data through convolutional processing. It contains three kinds of neuron layers: convolutional layer, pooling layer and fully connected layer. Among them, the convolutional layer can extract features from data, the pooling layer is generally used to reduce the dimension (complexity) of data, and the fully connected layer uses the information learned from the first two layers for classification. However, DL technologies cannot be applied to detect and distinguish well for all types of cancer. [31–33].

Despite multilayer perceptron (MLP), recurrent neural network (RNN) and CNN are the most fundamental and are frequently used as building blocks for more advanced techniques, there are also many other types of AI technical methods with different advantages and applications. They are either used to analyze medical images, such as X-rays, CT images, etc. or to analyze molecular level data, such as gene mutations, gene expression data, etc. Especially optical imaging combined with AI-assisted analysis techniques such as computer vision and natural language processing (NLP), has also emerged as a powerful tool for improving the accuracy and efficiency of cancer detection, diagnosis, and treatment planning. Computer vision, a branch of AI, enables the analysis and interpretation of visual data captured through optical imaging techniques such as microscopy, endoscopy, and radiology. In the realm of cancer diagnosis, computer vision algorithms have revolutionized image analysis, aiding in the detection of suspicious lesions, tumor segmentation, and classification. By leveraging advanced image processing techniques, computer vision algorithms enhance the detection sensitivity and specificity, contributing to earlier and more accurate cancer diagnoses. Additionally, computer vision plays a vital role in the identification of treatment response and monitoring disease progression over time. In the context of cancer therapy, NLP techniques facilitate the extraction of valuable information from medical literature, clinical reports and patient records. By analyzing vast amounts of unstructured text data, NLP algorithms can aid treatment decision-making, clinical trial identification, and personalized patient care. NLP-powered tools can extract relevant information from medical texts, including research articles, clinical guidelines, and case studies, providing oncologists with a comprehensive knowledge base to guide their treatment strategies. Furthermore, NLP can assist in the automated summarization and interpretation of patient data, reducing the cognitive load on healthcare professionals and enabling more efficient and accurate treatment planning. The integration of computer vision and NLP techniques in AI-assisted optical imaging has shown promising results in cancer diagnosis and therapy. By combining the power of image analysis with text mining, these approaches allow for a more holistic understanding of cancer-related information. For instance, computer vision can extract visual features from medical images, while NLP algorithms can extract pertinent clinical and genomic information from patient records. The fusion of these data streams can lead to more comprehensive and personalized diagnostic reports, enabling healthcare professionals to make well-informed treatment decisions. While AI-assisted optical imaging has demonstrated immense potential in cancer diagnosis and therapy, several challenges need to be addressed. Interpreting complex and heterogeneous data, ensuring data privacy and security, and integrating AI systems seamlessly into clinical workflows are among the key challenges. Furthermore, the need for extensive and diverse datasets, regulatory considerations, and addressing biases within the algorithms are essential aspects to be considered for ethical and responsible AI deployment. AI-assisted optical imaging, employing computer vision and NLP techniques, has emerged as a powerful ally in the fight against cancer. By leveraging these advanced technologies, healthcare professionals can improve accuracy, efficiency, and personalized care in cancer diagnosis and therapy. As we continue to refine and expand these techniques, AI-assisted optical imaging holds tremendous promise for transforming the landscape of cancer care, ultimately leading to

improved patient outcomes and a brighter future in the battle against cancer.

2. Development of artificial intelligence in medical imaging

The development of AI-aided medical imaging could trace back to 1963, when Gwilym S. Lodwick et al. [34] reported their progress in the development of a program-aided diagnosis of bone cancer and proposed 5 requisites for programming diagnosis to achieve an optimal diagnostic accuracy based on their initial application experience. Six months later, they demonstrated a method of coding roentgen data in numerical form for high-speed processing. The effectiveness of this coding system for describing roentgenograms has been proved through reconstruction of the original image from coded data derived from applying to 541 cases of lung cancer, suggested that the development of such a coding system makes possible the exploration of the use of the digital computer as an aid in radiologic diagnosis [35]. Then research on this concept was underway. In 1964, it was reported that the computer automatically read and analyzed the cardiothoracic ratio [36], and abnormalities in mammograms were autodetected by means of optical scanning and computer analysis in 1967 [37]. In 1975, Stanford University made a consultation program named MYCIN, which offers advantages over Bayesian analysis when they are utilized in a rule-based computer diagnostic system, which never failed to cover a treatable pathogen while demonstrating efficiency in minimizing the number of antimicrobials prescribed [38,39]. The study design may be useful in assessing the performance of other computer-based clinical decision-making systems. Even with all these advances, medical imaging AI was still limited by that the computer performance was insufficient to address complex issues and unable to acquire sufficient data for intellectualization at that time. With the holding of the first International Conference on Machine Learning in 1980 s and the proposal of effective training methods namely backpropagation algorithm-based computational model of convolutional neural network in 1989 s [40], the AI revived through substantial pioneering efforts in computer-aided diagnosis and identifying subtle change that was easy to be overlooked by physicians. By using AI in medical imaging, physicians can identify conditions much quicker, promoting early intervention, while with limited applications and exposure of commonsense errors, AI failed to perform well in complex problems. However, in 1997, it's the first time that computer called Deep Blue beat world chess champion Garry Kasparov, whose victory was hailed as a milestone for AI. And with constant development of medical imaging, AI technology, especially the propose of DL since 2006 [41], the clinical application of these two technologies have made great progress and AI research and application entered the outbreak phase. Later in 2012, a convolutional neural network model called AlexNet succeeded in bringing down the error rate and has greatly improved the ability of computers to recognize images without any unsupervised pre-training [42]. Five years later, AlphaGo that combined Monte Carlo tree search engine with two deep neural networks defeated world Go champion Lee Sedol [43], which boomed the universal attraction and much more investment in AI.

With the expansion of medical image database and AI algorithm optimization as well as the ascension of the hardware and software such as central processing unit, graphics processing unit and cloud storage and transmission techniques, AI-aided medical imaging took the medical world by storm. Food and drug administration (FDA) of United States started implementation of the digital health innovation initiative and accelerated approve of patented medical imaging AI algorithms in 2018. Especially the first AI cancer diagnosis platform belong to Paige.ai company established on a dataset containing 5 million digitalized pathological sections approved by FDA, marked that the commercialization of AI in cancer diagnosis entered into a new era [44,45]. And Paige.ai company confirmed that its AI pathology system had achieved "near perfect" accuracy in detecting prostate, skin and breast cancer, declaring it "the world's first clinical-grade AI application for pathology." in 2019 [46]. Great importance is also attached to national medical products administration of China, which emphasized the new generation of AI-assisted medical devices in workflow optimization, data processing, auxiliary diagnosis and so on that refers to the AI of data-driven algorithm training represented by DL and neural networks. Currently, in many kinds of medical imaging conditions, AI has reached the level of medical experts [47], and more and more autonomous AI system including standalone medical software acquired approve to provide clinical diagnostic decisions [48,49], which means medical imaging AI has switched from reading pathological data to clinically meaningful endpoints [22]. In 2017, Google Healthcare's AI system outperformed professional pathologists in diagnosing breast cancer and next year they released an AI detection system for advanced breast cancer that can correctly distinguish metastatic cancers in 99% of the time. In 2020, Google Health and DeepMind have built a new AI system that can analyze and process largescale breast cancer X-ray angiography data, paving the way for further clinical trials [50]. It is estimated that 90% of cancer deaths occur because the cancer has metastasized to other parts of the body. Another representative company named Volastra Therapeutics has a collaboration agreement with Microsoft to jointly develop machine learning tools to discover factors driving tumor growth and predicting metastasis risk using its Azure AI system in 2021. Even though there are still many challenges involved in physician responsibility and defective regulatory policies and safety monitoring for AI products, AI showed great promises in medical imaging so as to help doctors improve the diagnostic efficiency and diagnostic accuracy, shorten the waiting time to the patient, reduce the medical treatment cost, etc. And important development timeline of AI-aided medical imaging was sorted out in Fig. 3.

3. Application of artificial intelligence to the diagnosis and therapy of cancer

3.1. Artificial intelligence for cancer pathology

In the discovery of body abnormalities, pathology is a key step of cancer theranostics that primarily based on optical imaging like brightfield microscopy. Almost every patient who receives a cancer diagnosis will have a histological section. The first step of AI application in cancer pathology relies on capturing the histopathological images with high-resolution and high speed, otherwise there will be a serious dilution of morphological and tumor markers evaluation. Conventional visual assessment to extensive glass slides of tissue slice or biopsies stained with hematoxylin and eosin, immunohistochemistry or special stains by pathologists face the problems of subjectivity, low reproducibility and misdiagnosis, whose dilemma was solved with the invention of a fully automatic digital scanning microscope and the approval of whole-slide scanning system [51]. So far, whole-slide imaging system has been an essential tool for hospitals, disease control centers, new drug development and scientific research institutions, particularly the AI enhanced whole-slide imaging system has almost transformed the cancer pathology from simple slice digitalization to high-throughput photography with automatic image analysis like extremely accurate image classification or segmentation and quantitative biomarker evaluation [52] that perform on par with or even outperform pathologists (Fig. 4), which greatly advance differentiation of cancer from normal tissue, diminutive polyps metastases detection [53–55], clinical decision-making, therapeutic response and prognosis prediction and significantly reduce false-positive rate and overdiagnosis.

In recent years, application of ML especially DL further prompted the wider use of AI cancer pathology in daily clinic practice. Training of traditional image analysis model require labels from time-consuming manual annotation of digitized slice images, such as defining cancer or metastasis. While ML can apply statistical methods to optimize a model for a specific task without relying on a specific human orientation to define all the rules or parameters in the model. Though previous

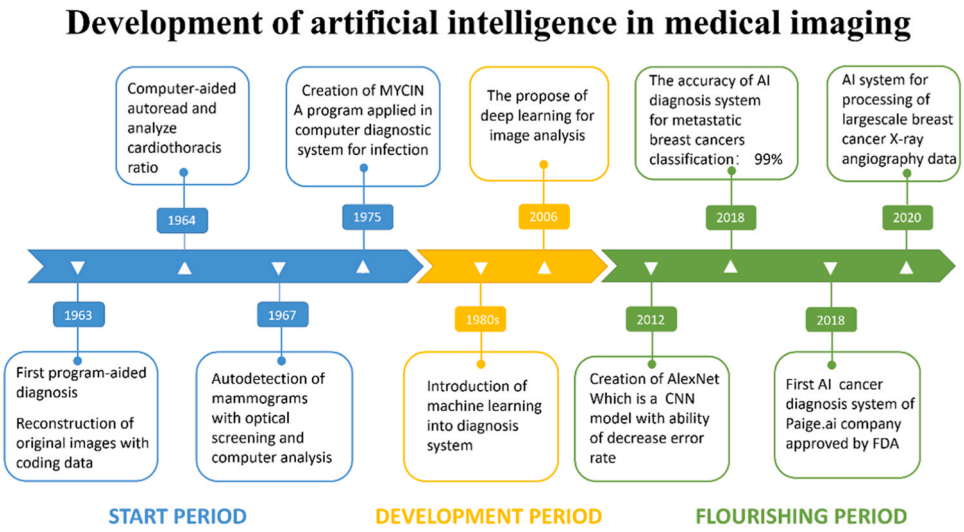

Fig. 3. Timeline of major nodes in AI-assisted medical imaging.

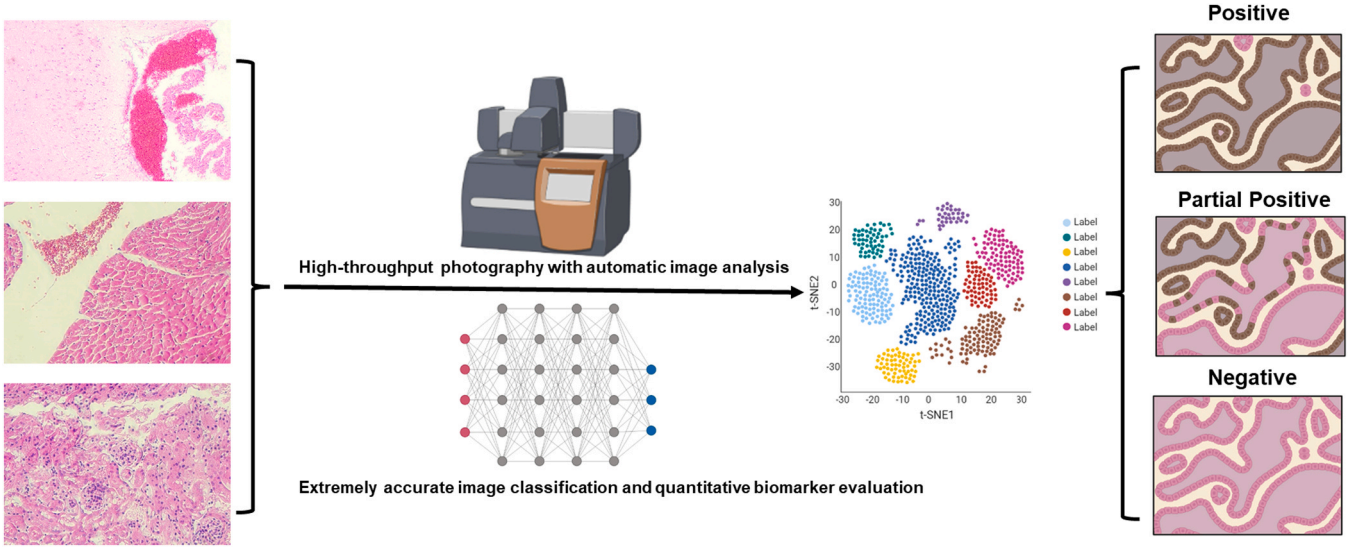

Fig. 4. High-throughput histopathological photography with automatic image analysis is noninferior to pathologists on cancer diagnosis, including biopsies and resections stained with hematoxylin and eosin, immunohistochemistry and special stains, which is valid across a wide range of organ systems, sampling methods, specimen types, stains, and practice settings.

generations of ML-based image analysis models have relied on human feature engineering, its subset namely DL holds an inherent part of feature extraction that auto-optimize to learn representations directly from data [56]. Once the model has been optimized on large amounts of training data, the learning patterns captured by the model can be applied to predict responses or labels in previously unseen observations. In that case, given the large training dataset, slice-level labels, such as the presence or absence of cancer, may be sufficient to train high-performance DL models. Ultimately, the architecture and properties of deep neural networks facilitate the modeling of highly complex and nonlinear patterns in the data and have excellent performance in many cases. Recently, a novel decentralized AI technology named swarm learning (SL) was developed and has been successfully used in a large, multicenter histopathology image dataset of more than 5000 patients, and SL-trained AI models can predict clinically relevant genetic changes directly from images of colorectal tumor tissue. In addition, researchers are able to train AI models using small datasets through SL, reducing hardware requirements, enabling the training of independent AI algorithms for different image analysis tasks without data transfer [57].

In cancer, the complexity of genomic alterations that affect cellular signaling and the interaction of cells within their microenvironment can influence the biologic processes of the disease and response to therapeutic interventions [58]. Digital histopathological images contain a large amount of clinically relevant information, and AI can directly predict molecular changes from conventional histopathological slides. To provide a systematic understanding of the cellular and biological consequences of human genetic variation and of the heterogeneity of such effects among a diverse set of human tissues, the genotype-tissue expression consortium successively established large deep datasets to map the genetic regulatory effects in different human tissues [59,60], and demonstrated that multi-tissue, multi-individual data can be used to identify genes and pathways affected by human disease-associated variation. In addition, AI has increasingly been applied to assess cancer severity and predict therapeutical outcomes. In particular, CNN was used to integrate information from both histology images and genomic biomarkers to predict the overall survival of patients diagnosed with glioma with accuracy that surpassed the current clinical paradigm for

predicting [61]. Meanwhile, AI-assisted diagnosis and grading of prostate cancer [62–65], and detection of breast cancer nodal metastasis [66] in histopathological or biopsies slides could be achieved by machine learning. While machine learning-assisted pathological recognition has been focused on supervised learning that suffers from a significant annotation bottleneck, so Gang Yu et al. proposed a semi-supervised learning method can accurately detect and diagnose colorectal cancer from tissue scans as well or better than pathologists [67]. The application of DL for automated segmentation (delineation of boundaries) of histologic primitives (structures) from whole slide images can facilitate the establishment of novel protocols for kidney biopsy assessment and segmentation of histologic structures in the kidney cortex with multiple histologic stains as well as near real-time intraoperative brain tumor diagnosis [68].

Despite these promising reports, there is still a long way to go from experiments to clinical practice [69]. Standardization of data format and normalization method of data analysis may promote sharing datasets from different resources that reduce variation in classification accuracy and accelerate model-training maturity [70], besides the digitalization of the whole process, including the interconnection of embedding machine, dehydrator, dyeing machine and sheet sealing machine, aiming to realize precision pathology that is more accurate, more efficient, more convenient and lower cost.

3.2. Artificial intelligence for cancer monitoring and diagnosis

It has been more than thirty years that AI was used to conduct cancer monitoring and diagnosis, while early attempts did not yield satisfactory results due to prevailing condition of limited computer performance and lack of available data. With remarkable development of AI particularly DL with much higher accuracy because it can automatically extract richer and more useful information from the data, AI-aided medical imaging on cancer monitoring and diagnosis shows great potential to increase both quantity and quality of patient life (Fig. 5) [71–73]. Radiomics is a process which can convert digit medical images into mineable data. Subsequent analysis plays an important role in clinical decision making. Radiomics can supply numbers of biomarkers for cancer detection, diagnosis, prognosis and monitoring. What's more, combination with genomic and clinical data can be used for evidence-based clinical decision report. The processes of radiomics includes image acquisition, volume of interest identification, segmentation, feature exaction and qualification, building the database and classifier modeling and data sharing [74]. Due to massive amount data of radiomics, the integration of AI can increase efficiency and reduce the errors. Basically, there are two kinds of AI method applied in radiomics, which are traditional ML algorithms and DL method [75]. ML as a subfield of AI which can detect the hidden pattern based on some statistical methods. And DL is applied in classification, detection and segmentation of medical imaging on oncology and the performance is as accurate as that of clinical experts [76–78]. The traditional ML relies on predefined engineered feature algorithms with parameters based on expert knowledge. This method can increase the efficiency and optimize clinical decision. However, the weakness is obvious. First, due to the parameters are based on expert knowledge, the selection of parameters can't be optimized. Second, the predefined features can't adapt to different imaging modalities. While the DL method is a data-driven approach, which can automatically learn from data without role of human expert. It can automatically identify the kinds of disease. Compared with traditional ML method, DL method can adapt to various conditions and parameters and also weight up the parameters due to big data to help clinical decision [79].

In the context of AI for cancer monitoring and diagnosis, radiomics was proposed to unlock the hidden information contained within medical images that may not be visually evident to human observers. By leveraging AI algorithms, radiomics enables the extraction and analysis of a multitude of quantitative features from medical images, going beyond what is perceptible to the human eye. In clinical diagnosis and monitoring, AI-aided radiomics can effectively integrate with multimodality imaging as well as genomic and clinical data [80]. In 2021, Aggarwal R et.al evaluated accuracy of DL in medical imaging. The meta-analysis result showed great potential but lack of standardized guidance around study design and reporting. What's more, the kinds of imaging applied in clinic is limited. With the emerging of optical imaging, the techniques of diagnosis and monitor are more diverse. The optical imaging is molecular sensitive, nonionizing, large size scales and so on [81]. The adding of optical imaging in radiomics can effectively optimize the clinical decision making. Due to relative works, the AI-aided radiomics with optical imaging shows great potential in both

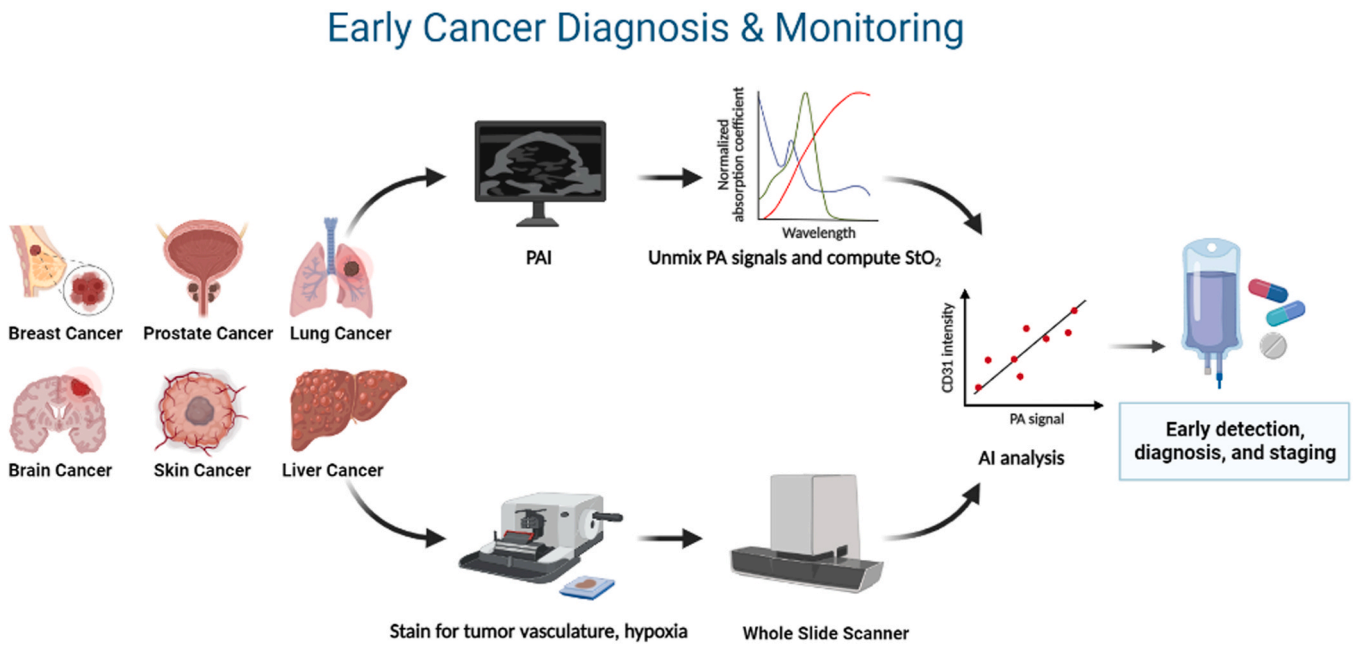

Fig. 5. AI automatically extract richer and more useful information from the optical images, whose cancer monitoring and diagnosis shows great potential to increase both lifespan and quality of patient life.

cancer diagnosis and monitoring. Andre Esteva, who published a breakthrough in Nature this year, has designed a CNN that can diagnose skin cancer with an accuracy that exceeds or even exceeds that of dermatologists. They used the GoogleNet Inception V3 CNN framework, which had been pre-trained with 1.28 million images, and then trained 130,000 medical images covering 2032 diseases with transfer learning techniques that eventually enabled the CNN to classify images as one of 757 skin diseases, including skin cancer. It also has the advantage of being able to analyze ordinary photographs directly, without requiring medical images or preprocessing, as previous studies have done. What's more, the technology is expected to be deployed on mobile devices in the future, meaning users will be able to take a picture of a suspicious area with their phone and know if it's cancerous, rather than having to make a trip to the doctor. The authors estimate that by 2021, about 6.3 billion smartphones worldwide will be connected to the system, providing low-cost, accurate skin diagnosis services to the public [82].

CNN are also used in genetic information analysis to find gene mutations or changes in gene expression. It is well known that cancer is caused by genetic mutations in cells. Therefore, the gene sequence and gene expression pattern of cancer cells are different from that of normal cells, which provides us with a diagnostic basis. In theory, genetic testing is the best way to detect cancer because the behavior of cells is ultimately controlled by genes. Direct detection of genetic abnormalities can lead to early detection of cancer, and there is much effort in the scientific community, such as the ongoing "precision medicine" initiative, to use genetic information to improve the effectiveness of clinical diagnosis and treatment. But testing for mutations and gene expression information can be much more expensive than medical imaging. What's more, the message from genetic testing is much more subtle, and the link between gene expression and cancer requires a lot of research to know the exact relationship between genes and cancer. Therefore, there are not many relevant studies in this area at present. Notably, in 2017, Yuan developed DeepGene, a deep neural network-based technology that can analyze a patient's genetic mutation data and identify which type of cancer they belong to. After filtering irrelevant genes and reducing data sparsity from gene sequencing data, DeepGene uses a deep neural network to determine which type of cancer it is. Although it can achieve higher accuracy than some previous methods, such as SVMsand Naive Bayes, it is only about 60% [83]. Xiao designed a method combining multiple machine learning models and deep neural networks to identify gastric cancer, lung cancer and breast cancer based on gene differential expression data, but the accuracy was not high [84].

The primary site of tumor origin of about 1∼2% cancers cannot be identified and the median overall survival was only 2.7–16 months, posted a huge challenge to treatment that only target primary tumors. To solve this thorny problem, Faisal Mahmood's team developed a DL-based tumor-origin prediction system for cancers of unknown primary called TOAD, which can simultaneously identify whether the tumor is primary or metastatic and predict the site of its origin. The model was trained using tumor gigabixel caseology whole-slices from more than 22,000 cancer cases, and TOAD was then detected in approximately 6500 known primary cases and analyzed for increasingly complex metastatic cancer cases to build an AI model for an unknown primary cancer. For tumors of known primary origin, the model accurately identified the cancer within 83% of the time and placed the diagnosis in the top three predictions 96% of the time. In 317 cases test of primary unidentified cancer with differential diagnosis, it was found to agree with the pathologist's report in 61% of the time, and with the top three predictions in 82% of cases [85], indicating that TOAD can help improve the diagnosis of patients with complex metastatic cancer.

In addition to these cancer categories, AI is also designed to analyze different medical images to detect cancers such as osteosarcoma, head and neck cancer, bladder cancer, brain cancer, and oral cancer.

3.3. Artificial intelligence for cancer treatment and prognosis

AI allows rapid and low-cost access to new drugs and treatments. AI integrated diagnostics and biological big data containing genomics, proteomics, metabonomics and radiomics provides powerful supports for clinic decision-making and cancer treatment planning, monitoring, administration and optimization based on outcome prediction that can make much better prognosis [86]. And AI is promising to be applied to the entire medical industry over the next few years (Fig. 6).

AI could boost personalized cancer treatment based on patient data. The efficacy of the same treatment may vary from patient to patient, so the development of personalized treatment based on patient data is necessary. From machine learning to neural networks, AI platforms can accelerate drug discovery, accurately match patients to appropriate clinical therapies using biomarkers, and truly personalize cancer care using patients' own data. The performance of reinforcement learning in drug design was strong, with reinforcement learning using rewards and punishments to train the algorithm to obtain the desired drug structure successfully designing a new compound in 21 days, compared to a traditional timeline of about 1 year. Furthermore, the subsequent observed pharmacokinetic properties of the designed compounds indicate that they can achieve drug exposure (drug exposure refers to the degree of exposure to drugs, including time and intensity, as evaluated by AUC, Cmax, Tmax, etc.). And efficacy threshold can be used for the next step of lead compound evaluation. AI can also be used to recruit patients hierarchically. The inclusion of biomarkers in study recruitment improved patient outcomes compared with traditional stratified information, such as pathology or response to prior treatment. Stratification of recruited patients in combination with patient biomarker data and electronic health records (EHRs) may further influence trial results. AI will also play a key role in the delivery of cancer treatments. The maximum tolerated dose eliminates drug-sensitive tumor cells. However, resistant cells can eventually lead to treatment failure. To address this challenge, game theory is being explored, with dose-reducing algorithms competing with tumors to prevent drug-resistant cells, which have a high energy cost, from outnumbering drug-sensitive cells. This is known as adaptive therapy, which may prolong the effect of treatment by maintaining a threshold of drug-sensitive cells in the tumor to combat the proliferation of drug-resistant cells.

AI represents a gateway to the next frontier in cancer treatment, but there are drawbacks. For example, the combination of AI-optimized compounds with other therapies is not ideal, or the medication is not correct, and it is unlikely to significantly improve patient outcomes. Overcoming this challenge in oncology will require seamless implementation of AI across areas such as discovery, development, and management. Potential downstream applications include increasing the resolution of personalized care by tailoring customized programs that integrate multiple treatment strategies. For example, AI optimizes radiotherapy dose and maintains strong tumor size control, potentially combining with AI-driven drug administration. Ultimately, the full application of AI to clinical oncology practice may improve drug access and reduce healthcare costs. As AI continues to be validated and pathways to widespread practice are identified, its potential to redefine clinical standards for cancer care is becoming increasingly apparent [87]. Asked four experts for their opinions on how we can begin to implement AI while ensuring standards are maintained so as transform cancer diagnosis and the prognosis and treatment of patients with cancer and to drive biological discovery. [88].

Cancer treatment and prognosis rely on the accurate diagnosis and wise decision-making, which requires consecutive assessment to dynamic tumor-microenvironment changes in a highly accurate way while considering multiple characteristics simultaneously. AI-aided optical imaging that noninvasively snatches tumor phenotypes and hints at potential pathophysiological changes based on biomarkers plays an important role in stratifying degree of tumor malignancy, prediction of therapeutic outcomes and qualitative and quantitative of tumor-

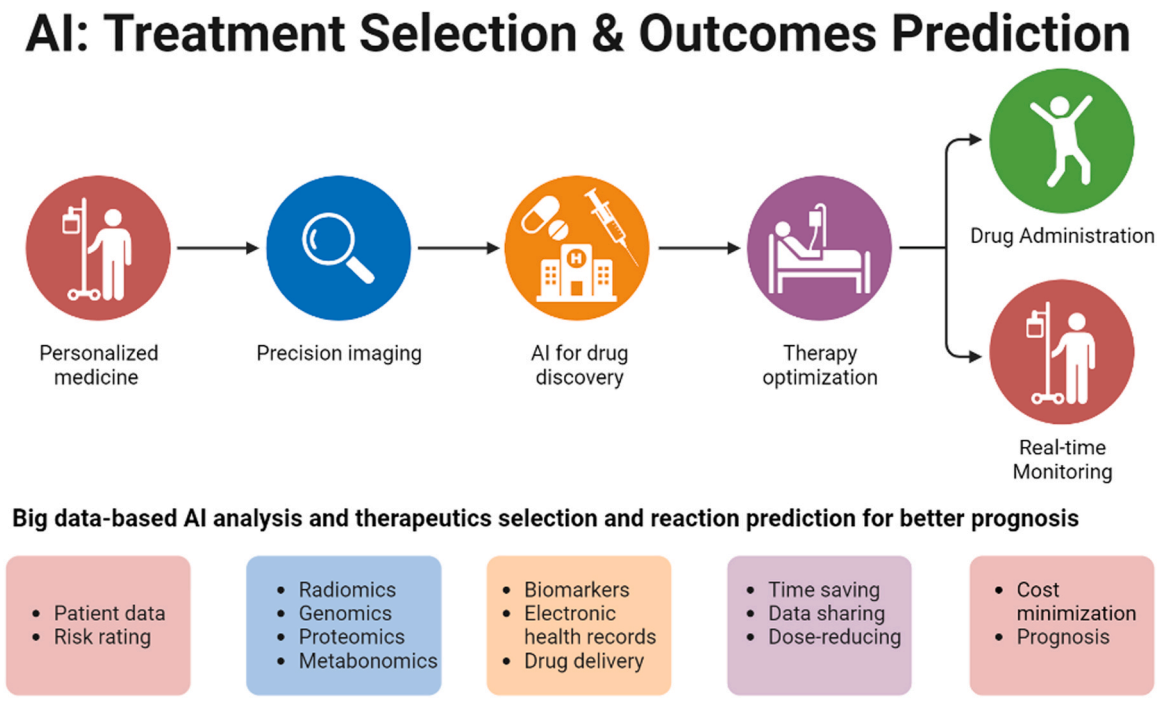

Fig. 6. The application of AI in cancer treatment and prognosis.

heterogeneity analysis that closely related to prognosis. AI could monitor the whole process of tumor treatment over time and record a staggering number of tumor characteristics that real-time reflect tumor development and efficacy [89], while traditional tumor surveillance is often limited to tumor volume. Machine learning could be used to mine omni-imaging information with molecular and pathological data that strengthen the ability of physicians to detect, locate and manage the cancer, which could be used for screening and developing targeted drug and optimal personalized therapy regimens, as well as predicting cancer outcomes [62]. Molecular data such as genome, DNA methylation, mutation, m6A and single cell sequencing data are often used to characterize the tumor-related features that produce profound changes in the occurrence and development of tumors. By identifying risk factors, AI-aided optical imaging system can determine an individual's likelihood of developing certain cancers, then physicians can encourage patients to take preventive care strategies. JY Liang et al. developed a novel cancer AI survival analysis system to provide individual mortality risk predictive curves for cervical carcinoma patients based on three different AI algorithms, which could provide mortality percentage at specific time points and explore the actual treatment benefits under different treatments in four stages, which could help patient determine the best individualized treatment [90].

AI-based automated radiotherapy planning strategies have been proposed in lots of cancer sites and are the future of treatment planning. Thereinto, postmastectomy radiotherapy decreases local recurrence probability and improves overall survival, and volumetric modulated arc therapy (VMAT) has gradually become the mainstream technique of radiotherapy. S Jiang et al. developed an AI-based automated treatment planning method for postmastectomy VMAT to ensure plan quality and improve clinical efficiency [91]. The rise of AI has also given new vitality to liver cancer surgery, as well as individualized treatment experience and greater healing opportunities for patients [92]. In addition to immunotherapy, other therapies (e.g., targeted therapy and neoadjuvant chemotherapy) have achieved prominent clinical success in specific populations, driving the need for accurate predictive assays to inform patient selection. This requirement can be met by a combination of big data and AI [93]. Nanomedicine design also benefits from the application of AI, by optimizing material properties according to predicted interactions with the target drug, biological fluids, immune system, vasculature, and cell membranes, all affecting therapeutic efficacy [94]. Triboelectric nanogenerator with AI based systems will also be a potential candidate for applications in the field of cancer management and prevention [95].

Using deep transfer learning, the research team quantified histopathological patterns in 17,355 histopathological images from 28 cancer types and correlated them with matched genomic, transcriptomic, and survival data. Computational histopathologic features have been found to be associated with a large number of recurrent genetic aberrations in multiple cancer types, including genome-wide duplications across cancer types, single chromosome aneuploidy, lesion amplification and deletion, and ubiquitous features in driver gene mutations. Computer vision has great potential to characterize the molecular basis of tumor histopathology, highlighting the potential of AI to improve cancer diagnosis, prognosis, and treatment [96].

AI will promote drug discovery and development because AI is favorable to solve the toughest problem of extremely high clinical failure rate through prediction on toxicity of candidate drugs to animal and human and pharmacokinetic/pharmacodynamic index that can save billions of dollars, improve R&D efficiency and shorten several years process of drug discovery and verification, which has been gradually materialized by many top pharmaceutical companies like GlaxoSmithKline and Takeda. In the other hand, unpublished and failed experimental records as well as negative data are mined through machine learning to revalidate and optimize synthesize routes of drugs based on decision trees and support vector machines, which outperformed traditional human strategies and successfully predicted conditions for new organically templated inorganic product formation with a success rate of 89% [97]. Yet another example of how AI can reshape industries and change the world is the accurate prediction of protein structure by AlphaFold2. AI is an advanced approach to identify novel anticancer targets and discover novel drugs from biological networks because the network can effectively preserve and quantify interactions between components of the cellular system underlying human diseases such as cancer. Artificial intelligence models provide us with a quantitative framework to investigate the relationship between network features and cancer, leading to the identification of potential anticancer

targets and the discovery of novel drug candidates [98]. For cancer therapies, dozens of new treatments enter clinical trials each year, but less than 4% are ultimately approved by the FDA. Although there are many factors contributing to this result, the main problem is that we don't fully understand how or why specific cancers respond to treatment. Therefore, it is currently not possible to combine the right drugs in the best way and match them to the right patients. But the advent of AI may give us a leg up. Most machine learning models are "black boxes" that can be optimized for accuracy without needing to understand or care about the biology of their predictions. Created a new artificial intelligence (AI) system called DrugCell, which makes it possible to match tumors with the best drug combinations. With DrugCell, after entering data about the tumor, the system returns the best-known drug, the biological pathway that controls the response to that drug, and the best combination of drugs. DrugCell combines the inner workings of models with the hierarchy of human cell biology so that it can predict the response to any drug in any cancer and design effective combination therapies. The results showed that DrugCell could accurately predict cell line response to treatment (Spearman correlation coefficient =0.80 for total accuracy of all cell line-drug pairs). In addition, the predicted combination improves progression-free survival in patient-derived xenograft tumor models and can stratify clinical outcomes in patients with ER-positive breast cancer. DrugCell has been trained on the response of more than 1200 tumor cell lines to nearly 700 FDA-approved drugs and experimental therapeutic agents, for a total of more than 500, 000 cell line/drug pairs. While 1200 cell lines is a good start, it does not represent the complete heterogeneity of cancer. The research team is now adding more single-cell data and experimenting with different drug structures. They also hope to work with existing clinical studies to embed DrugCell in diagnostic tools and test it prospectively in reality [99]. In a new computational framework named EagleC that uses chromatin capture technology to identify genomic structural variation based on DL, AI showed potential application value for discovering new gene fusion events, assisting tumor typing and designing targeted therapeutic drugs [100].

4. Artificial intelligence-aided optical imaging for cancer theranostics

4.1. Optical Endoscopy

Optical endoscopy is commonly used as diagnosis and therapeutic tools for gastrointestinal (GI) cancer, including esophageal cancer, gastric cancer, colorectal cancer and so on [101–103]. AI-assisted endoscopy mainly focuses on two fields of endoscopy, including computer aided detection (CADe), computer-aided monitoring (CADm) and computer aided diagnosis (CADx) [104]. The fundamental principle of AI-assisted endoscopy is based on machine learning, which can teach the computer to recognize pattern in video or imaging data. What's more, as a fast-growing subfield of machine learning, DL attracts much more attention due to great properties, like high efficiency, high accuracy and so on [105]. In diagnosis of gastric cancer, AI showed higher detection rate of gastric cancer (100%) than that of expert endoscopists (94.12%), which showed great potential of AI-aided endoscopy [106,107].

Atsuo Yamada et.al utilized artificial intelligence into colon capsule endoscopy (CCE) to detect colorectal neoplasias including polyps and cancers. They extracted 15,933 images of colorectal neoplasias and trained the deep convolutional neuron network (CNN) with 4784 images which inculded 1850 images of colorectal neoplasias and 2934 normal colon images. In result, the area under curve of AI model for detection of colorectal neoplasias was 0.902 (95% confidence interval [CI]: 0.989–0.901). The sensitivity was 79.0% (95% CI, 77.1–80.9%). The specificity was 87.0% (95% CI, 85.7–88.2%). The accuracy was 83.9% (95% CI, 82.9–85.0%). The results showed that the automatic identification of CCE image to detect colorectal neoplasias still had some limitations, including the quality of image, difficulty on focusing, orientation problem, the properties of lesions and so on. In conclusion, the application of artificial intelligence into CCE images can reduce the burden of doctors in clinical utility but still need to be developed [108].

Esophageal cancer as a kind of GI cancer, has poor diagnosis and prognosis. Based on that, Yoshimasa Horie et.al constructed an AI-based diagnostic system of esophageal cancer through DL method. They collected 8428 training images of esophageal cancer lesions and prepared testing set with 1118 images to evaluate diagnostic accuracy. For construction, they used deep neural network architecture called Single Shot Multi-Box Detector. The constructed CNN system took 27 s to analysis 1118 test images. The sensitivity was 98%. And the diagnostic system could distinguish superficial esophageal cancer and advanced cancer with high accuracy (98%). But for each image, the positive predictive value is only 40%. In general, the result showed the potential of AI-based diagnostic system [109]. Rie Miyaki et.al constructed support vector machine (SVM)-based analysis system to detect early gastric cancer by laser-based endoscopy. In this study, they not just applied artificial intelligence but also develop endoscopy techniques. They combined them together for quantitative diagnosis for early gastric cancer. The new endoscopy system could capture both white light-images and blue-laser images (BLI). The BLI mode was brighter and could acquire mucosal surface information. In this system, SVM with a linear kernel was used as the classifier and the different output was used for image quantization. In this result, the SVM output values of reddened lesions and surrounding tissue significantly differ to SVM output values of cancer lesions. The results showed the system can distinguish early gastric cancer [110].

4.2. Optical Coherence Tomography

Optical coherence tomography (OCT) is a non-invasive, non-ionizing and label-free optical imaging method that can generate the two-dimensional and three-dimensional structural and functional images of biological tissues in vivo, in situ or real-time with millimeter penetration depth and micrometer resolution, which is widely used both in research and clinical practice [111]. OCT techniques emerged as various kinds including time-domain, frequency-domain, full-field, quantum and Doppler OCT, Mueller-matrix optical coherence tomography and optical coherence computed tomography. Compared to imaging in the first near infrared biological window (650 −950 nm), OCT presented information-rich vascular images with a higher signal-to-noise ratio as well as better imaging contrast and penetration depth in the second near infrared biological window (1000 −1700 nm) [112]. OCT angiography based on the variable backscattering of light from the vascular and neurosensory tissue in the retina has been approved by the FDA in late 2016 [113]. With the help of AI, especially machine learning and DL, OCT acquired powerful image reconstruction algorithms and more intelligent image analysis techniques, which can not only diagnose ocular diseases but also detect cardiovascular diseases, nerve fiber tracts and neurovascular imaging and cancer theranostics like tumor margins and intraoperative precision identification and resection guidance [29, 114–122]. In a 10-year follow-on study, AI-based spectral domain OCT achieved a higher level of accuracy and sensitivity in detecting retinal fluid than retinal specialists, which is important for diagnostic, re-treatment, and prognostic tasks [123]. In another study, DL showed ophthalmologist-level achievement on optical coherence tomography images detecting sight-threatening retinal diseases [124]. Diagnosing clinically unclear basal cell carcinomas (BCC) can be challenging. Line-field confocal optical coherence tomography is able to display morphological features of BCC subtypes with good histological correlation [125,126].

ML and DL aided OCT imaging boosted cancer diagnosis, therapy and prognosis. OCT has been widely investigated in the field of oncology for identification of cancerous entities. Since the interpretation of OCT images requires professional training and OCT images contain information that cannot be inferred visually, artificial intelligence (AI) with

trained algorithms has the ability to quantify visually undetectable variations, thus overcoming the barriers that have postponed the involvement of OCT in the process of screening of oral neoplastic lesions [127]. A precise resection of the entire tumor tissue during surgery for brain metastases is essential to reduce local recurrence. Conventional intraoperative imaging techniques all have limitations in detecting tumor remnants. Hence, J. Moller et al. applied a machine learning algorithm using principal component analysis and support vector machines to the OCT scans for classification obtained a classification accuracy of 99.10%, which can prospectively provide the surgeon with additional information about the tissue, thus optimizing the extent of tumor resection and minimizing the risk of local recurrences [128]. To help clinical translation limited by processing the large volume of generated data, Y. Zeng designed a DL -based pattern recognition OCT system that automates image processing and provides accurate diagnosis potentially in real-time. The network is trained and tested using around 26,000 OCT images acquired from 20 tumor areas, 16 benign areas, and 6 other abnormal areas. A sensitivity of 100% and specificity of 99.7% can be reached, which can be used to give an accurate real-time AI-aided diagnosis of colonic neoplastic mucosa [129].

4.3. Photoacoustic Imaging

Photoacoustic imaging has become one of the most popular imaging techniques by virtue of its optical sensitivity and high spatial resolution in deep tissue and noninvasive and nonionizing rapid imaging means [130], which provide multiscale information on cancer microvasculature, metabolic function and pathological characteristics that greatly benefits preclinic and clinic cancer early diagnosis, monitoring and therapy. In particular, photoacoustic imaging broke through the long-standing limit of heavy optical scattering of optical microscopy (shallow penetration up to ~1–2 mm and poor depth-to-resolution ratio about 1/3) and reached new noninvasive imaging depth in living tissue up to 7 cm. Massively parallel functional photoacoustic computed tomography hemispherically around the human head can produce tomographic images of the brain with a 10-cm-diameter fields of view and spatial and temporal resolutions of 350 micrometers and 2 s, respectively [131]. By means of in vivo imaging depth of 4 cm by scanning the human breast within a single breath hold of 10 s, high-speed three-dimensional (3D) photoacoustic computed tomography (PAT) generated increasing interest for uses in preclinical research and clinical translation including tumor margin examination, internal organ imaging, breast cancer screening, and sentinel lymph node mapping, among others [132,133]. Further impactful applications on in vivo imaging from gene expression to humans were achieved with the machine learning aided image reconstruction and processing mainly owing to long-term sustained contribution of Lihong V. Wang's laboratory [134–139], who was the first to report functional photoacoustic tomography, 3D photoacoustic microscopy [140], photoacoustic endoscopy, photoacoustic reporter gene imaging, the photoacoustic Doppler effect, the universal photoacoustic reconstruction algorithm, microwave-induced thermoacoustic tomography, ultrasound-modulated optical tomography, time-reversed ultrasonically encoded optical focusing [141], nonlinear photoacoustic wavefront shaping, and compressed ultrafast photography (100 billion frames/s, world's fastest real-time camera), which allow us to build better models of complex and dynamic systems to greatly advance our understanding of some extremely rapid biological interactions and chemical processes [142]. By using standalone single-impulse photoacoustic computed tomography, Lihong V. Wang's group imaged in vivo whole-body dynamics of small animals in real time and obtained clear sub-organ anatomical and tracked unlabeled circulating melanoma cells (CTCs) [143], which is a key determinant of metastasis, are critical for determining risk of disease progression, understanding metastatic pathways, and facilitating early clinical intervention. And linear-array-based photoacoustic tomography system successfully imaged suspected melanoma CTCs in patients in vivo, with a contrast-to-noise ratios > 9 [144]. Then, the time-consuming problem of the iterative image reconstruction of photoacoustic computed tomography with compressed sensing was also improved by graphics processing unit-based parallel computation framework and achieved an image reconstruction speed 24–31 times faster than the central processing unit performance, whose feasibility has been verified by in vivo experiments on human hands [145]. Surprisingly, Wang's group [146,147] firstly introduced the ergodic cavity into photoacoustic imaging and accomplished the time reuse of multi-dimensional spatial information, which greatly simplifies the system and reduces the cost while maintaining the imaging quality. Because of its simple system and excellent performance, this technology has broad application prospects, especially in wearable medical devices for the detection of important physiological indicators and CTCs.

In recent years, photoacoustic imaging has been further improved in all aspects with the help of AI mainly including volumetric deep-tissue imaging, high-speed wide-field microscopic imaging, high-sensitivity optical ultrasound detection, and ML enhanced image reconstruction and data processing [148]. Data acquisition strategies of photoacoustic imaging commonly involved in sub-optimal sampling of the tomographic data, resulting in inevitable performance trade-offs and diminished image quality. To improve this problem, Neda Davoudi et al. [149] proposed a new framework for efficient recovery of image quality from sparse optoacoustic data based on a deep CNN, which enhanced the visibility of arbitrarily oriented structures and restored the expected image quality as well as eliminated some reconstruction artefacts present in reference images rendered from densely sampled data. Subsequently, they also developed a CNN approach for enhancement of optoacoustic image quality which combines training on both time-resolved signals and tomographic reconstructions. Reference human finger data for training the CNN were recorded using a full-ring array system that provides optimal tomographic coverage around the imaged object. The reconstructions were further refined with a dedicated algorithm that minimizes acoustic reflection artifacts induced by acoustically mismatch structures, such as bones. The combined methodology is shown to outperform other learning-based methods solely operating on image-domain data [150]. Then N. K. Chlis et al. introduced a DL approach with a sparse-UNET for automatic vascular segmentation in MSOT images to avoid the rigorous and time-consuming manual segmentation [151]. However, the current DL -based PAT methods are implemented by the supervised learning strategy, and the imaging performance is dependent on the available ground-truth data. To overcome the limitation, this work introduces a new image domain transformation method based on cyclic generative adversarial network, which is used to remove artifacts in PAT images caused by the use of the limited-view measurement data in an unsupervised learning way. DL also powered localization PA imaging, for 3D label-free localization optical-resolution photoacoustic microscopy, the required number of raw volumetric frames is reduced from tens to fewer than ten, and for the 2D labeled localization photoacoustic computed tomography, the required number of raw 2D frames is reduced by 12-fold [152].

In another hand, photoacoustic imaging (PA) combined with ultrasound imaging (US) often limited by the depth and wavelength dependent optical attenuation and the unknown optical and acoustic heterogeneities, so S. Agrawal et al. [153] developed a hybrid USPA simulation platform by integrating finite element models of light and ultrasound propagations for co-simulation of B-mode US and PA images, whose potential was demonstrated to generate large scale application-specific training and test datasets for AI enhanced USPA imaging. Notably, aimed to identify spatiotemporal changes that occur prior to development of interval cancers, the clinical translation of PAI is accelerating in the areas of macroscopic and mesoscopic imaging for patients with breast or skin cancers, as well as in microscopic imaging for histopathology [154]. And representative images on AI-aided various optical imaging for cancer theranostics was shown in Fig. 7.

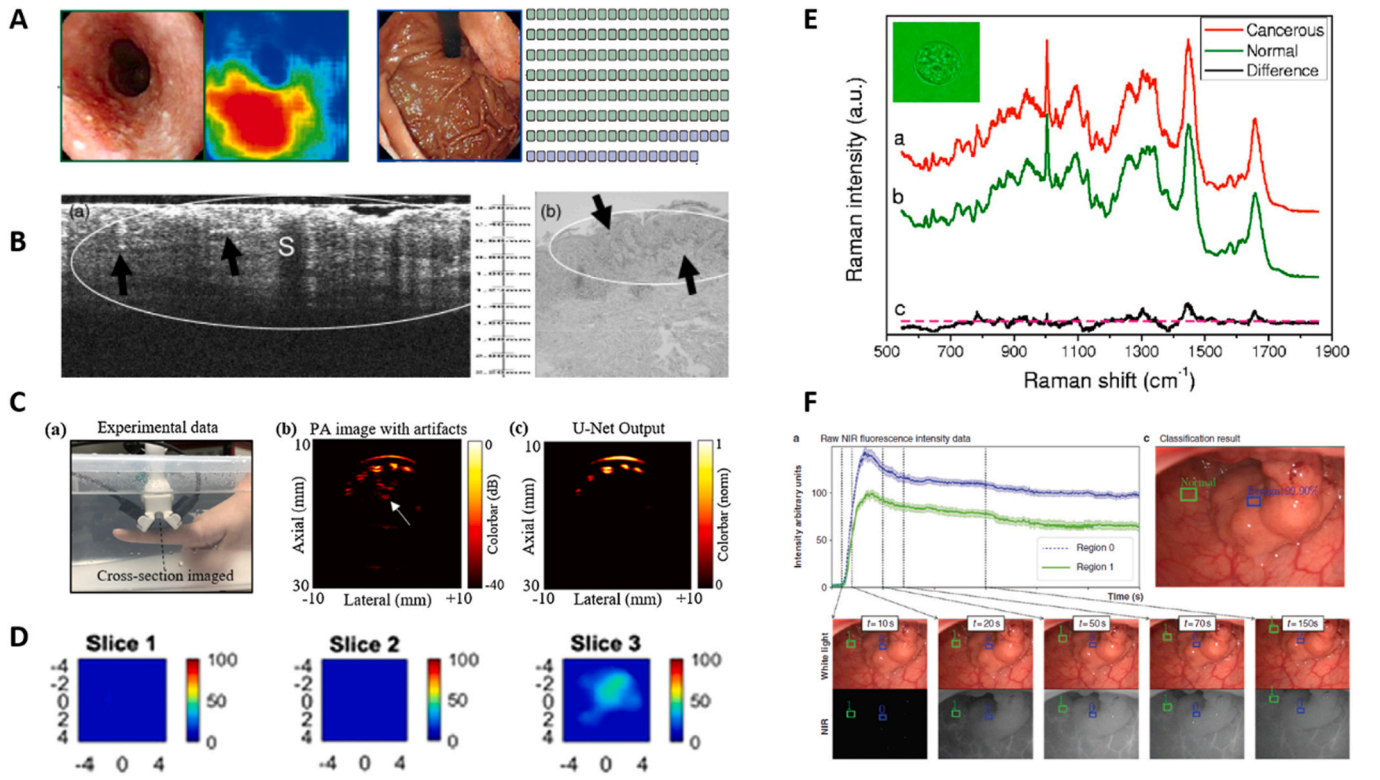

Fig. 7. Representative images on AI-aided various optical imaging for cancer theranostics. (A) Performance of gastrointestinal artificial intelligence diagnostic system compared with human endoscopists in identifying upper gastrointestinal cancers in test images from a randomly selected subset of patients (n = 175) from the prospective validation group. Copyright © 2019 Elsevier Ltd. (B) Machine-learning classification of non-melanoma skin cancers from image features obtained by OCT, which represented OCT-images of actinic keratosis (a) and corresponding histopathology (b). White bar indicate penetration depth. Black arrows point at white dots and streaks representing actinic changes. S is an artefact shadow due to overlying hyperkeratosis. Copyright © 2008 Blackwell Munksgaard. (C) PA simulation aided reflection artifact reduction using DL, in which (a) Picture of human finger immersed in water tank for PA imaging using a commercial LED-PAI system. (b) Acquired PA image with reflection artifacts (pointed with white arrow). (c) Output PA image obtained with DL (U-Net) approach. Scale: mm. Copyright © 2021 Elsevier GmbH. (D) Reconstructed DOT images from a 51-year-old woman with a triple receptor negative breast cancer and a high-grade invasive ductal carcinoma showed that this patient had a complete pathologic response with no malignant cells are identifiable in sections from the tumor bed. Copyright © 2018 SPIE. (E) Average spectra of the cancerous (a) and normal (b) cells in the training set and their difference spectrum (c=a−b). The inset is a photo of a captured epithelial cell. Copyright ©2007 SPIE. (F) Representative fluorescent image of process for intraoperative tissue classification illustrating benign and normal regions of interest, in which (a) Plot of continuous measured raw near-infrared (NIR) fluorescence intensity data for 180 s following administration of indocyanine green for two regions of interest (ROIs): blue trace (region 0) and green trace (region 1). (b) Still images from the white-light and fluorescence video with boxes showing ROIs for which data are being collected (top: white-light video sequence used for tissue tracking; bottom: corresponding NIR video sequence used for fluorescence intensity data acquisition). (c) Artifical intelligence classification results showing ROIs correctly classified as normal (green) and cancer (light blue), with classified regions superimposed on white-light video image.Copyright © 2021 Oxford University Press on behalf of BJS Society Ltd.

4.4. Diffuse optical tomography

Diffusion optical tomography (DOT) as a non-invasive imaging technique, is applied in breast cancer detection and characterization, functional brain imaging, muscle function imaging and so on [155]. Using near-infrared (NIR) light, DOT can construct 3D quantitative imaging of biological tissue by absorption and scattering properties of biological tissue [156]. DOT is able to detect and monitor the functional changes related to tumor angiogenesis [157]. DOT as one of the most complex optical imaging techniques, is still under development [158]. With the emerging of artificial intelligence, more AI-based image construction methods are developing. What's more, artificial intelligence also assist DOT in clinical application, which is similar to that of radiomics.

Due to the anatomy of breast and the sensitivity of DOT in hemoglobin oxidization level, DOT is applied into breast cancer detection. Due to the complexity of DOT, some AI-assisted construction algorithms are generating. Jaejun Yoo et.al [159] applied artificial intelligence into DOT and to overcome inverse scattering problem in DOT. In the imaging process, some individual photons could scatter many times or be absorbed by the medium due to physical properties of photon, which negatively affect the imaging tasks. That is called inverse scattering problem. In this study, the authors tried to solve the problem via DL method. The network designed to learn the complex non-linear physics in the inverse problem. The result showed that improved imaging construction. And without iterative procedure or linear approximation, the network can construct anomalies accurately.

On breast cancer, Yun Zou et.al designed a machine learning model with physical constraints in DOT system. In this study, the authors adopted multi-modality approaches by introduction of ultrasound into DOT system. More modalities mean more information as well as bigger data. Therefore, the introduction of machine learning was necessary, which can increase the accuracy of construction models in DOT. In machine learning approach, the model could learn from data and formulates and build the relationship with optical properties and measurements. The result showed that the model provided more accurate target sizes, maximum absorption coefficients, and depth profiles. Machine learning showed great potential on optimization of DOT algorithm [157].

Except for optimization of DOT algorithm, AI could be also applied in cancer diagnosis in DOT system. Qiwen Xu et.al designed a computer-aided diagnosis (CADe) system based on CNN, which is a network in

DL. CNN can simplify the steps in feature extraction. The system can classify breast mass lesions including benign breast tumor and a malignant breast tumor, which is obtained from DOT images. They collected 63 3D images from breast mass lesions of DOT system. They sliced one 3D images into 20 2D images for training and testing database. 75% of 2D images were for training and the rest of them is for testing. Although the dataset was small, the result showed that the system had great sensitivity and specificity. By training more data, it is promising to assist radiologist diagnosis breast cancer and screening the breast cancer [160].

4.5. Raman imaging

Raman imaging is a powerful, noninvasive, and non-contactual vibrational spectroscopic technique. As an optical surface scanning technique, it is capable of detecting endogenous biomolecules inside cells and tissues and used to detect changes in structure and composition during the dysplastic transformation of cellular components. A combination of Raman spectroscopy and microscopy has also been used to study biomolecular processes at the cellular level. Moreover, Raman microscopy may be used to diagnose diseases noninvasively because it offers features such as in vivo and ex vivo imaging, rapid spectral acquisition, superior molecular sensing, deeper depth profiling, and superior chemical sensitivity. Additionally, it has capabilities for 3D sectioning, non-label imaging, pharmacokinetics analysis, and in situ monitoring of diseases and drugs. Raman microscopy has been shown to be successful in biomedical applications because healthy tissues differ significantly from diseased tissues in terms of chemical composition. Furthermore, various tags have been examined for the identification, diagnosis, and control of disease development based on a fundamental understanding of chemical processes with Raman imaging and spectroscopic measurements. For example, Jiang Cheng et al. used stimulated Raman histology images of skull base tumor to train a CNN model using 3 representation learning strategies: cross-entropy, self-supervised contrastive learning, and supervised contrastive learning, which achieved overall diagnostic accuracy of 91.5%, 83.9% and 96.6%, respectively, implying that their model can segment tumor-normal margins and detect regions of microscopic tumor infiltration in meningioma SRH images [161].

Over the last decades, introduction of label-free Raman-based imaging techniques create the possibility of bringing chemical and histologic data into the operation room. Relying on the intrinsic biochemical properties of tissues to generate image contrast and optical tissue sectioning, Raman-based imaging methods can be used to detect microscopic tumor infiltration and diagnose tumor subtypes, in particular toward the development of imaging systems to detect pathologies [162–164]. Raman spectra are information-rich and can provide chemical fingerprints of cells, tissues or biofluids. The principle is based on an inelastic scattering process, also known as Raman scattering, according to which when incident light excites molecules in a tissue, the molecules will reflect light in a different wavelength. By monitoring the intensity profile of the inelastically scattered light as a function of frequency, the unique spectroscopic fingerprint of a tissue sample is obtained. Since each sample has a unique composition, the spectroscopic profile arising from Raman-active functional groups of nucleic acids, proteins, lipids, and carbohydrates allows for the evaluation, characterization, and discrimination of tissue type. This nondestructive optical technique does not need any pre-treatment or labeling of the tissue. This has considerable utility in surgical diagnosis.

Raman spectra accompanied by enhanced AI and ML have become powerful tools in prediction of disease more accurately. Recently, a combination of Raman microspectroscopy and artificial intelligence techniques have been used successfully in the identification of various cancers such as lung [165–167], breast [168–171], cervical [172], brain [173,174], skin [175–177], oral [178–180], tongue [181–183], prostate [184,185], nasopharyngeal [186,187], colon [188,189], ovarian [190] and kidney cancer [191]. Currently, the majority of the algorithms that use Raman spectroscopy for disease detection are based on traditional machine learning. Since Raman spectra are high dimensional, feature extraction is necessary before classification. At present it has become common practice for data analysis to begin with optimization of the raw input data using principle component analysis (PCA) and partial least-square analysis (PLS). Linear Discriminant Analysis (LDA) and SVMs with an appropriate kernel function are usually used as classification methods of traditional machine learning. DL's ability to capture non-linear complexities in a dataset allows them to exploit patterns too subtle for traditional methods, making them an ideal candidate to realize the full potential of Raman spectra. At present, the neural network models used for Raman spectra analysis are mainly CNNs. More complex models have also been used in Raman spectra analysis, for example, Leng et al. [167] proposed an improved ResNeXt model to achieve accurate classification of serum Raman spectra of lung cancer. Hence, AI-assisted Raman imaging has the capacity to probe very early biochemical changes that accompany malignant transformation, even prior to the onset of morphological changes, to produce a fingerprint of cancer and exhibited potential in vivo application in breast cancer in automatically analyzing both ex-vivo tissue and liquid biopsy samples.

4.6. Fluorescence imaging

Fluorescence imaging depicts the release of energy as light by a substance (a fluorophore) from an unstable excited state upon photons absorption to a ground state. Due to some energy loss during the brief stimulated lifetime, the emitted light typically has a lower energy (and thus a lower frequency) than the initial absorbed light. Fluorescence is an extremely sensitive technology because fluorophores can repeatedly go through excitation and emission, enabling them to generate a signal several times. The creation and emission of light by a live organism in bioluminescence imaging, in contrast, occurs when energy is released through a chemical process in the form of light. For instance, the enzyme luciferase catalyzes the reaction in which the substance luciferin combines with molecule oxygen to produce light. All kinds of fluorescent dyes greatly improved the contrast, signal to noise ratio and resolution of fluorescent imaging from molecular level. In an oncology case, fluorescence dye can be marked on a specific protein which only highly expressed in tumor tissue. This can provide valuable information for diagnosis and make this broad category of imaging instruments an important diagnostic tool [192–202]. Fluorescence microscopy is one of the essential instruments in biomedical research so as pathological diagnosis of cancer. Conventional optical microscopy can straightforwardly detect abnormalities in the tumor tissues and stained cell slide and diagnosis based on morphological features are reliable while still limited by imaging depth, narrow field of view and fluorescence quenching. However, the rapid advancement of two-photon excitation microscopy, laser speckle contrast imaging, Super-resolution microscopy, in vivo fluorescence imaging and near-infrared the second biological imaging has thoroughly enriches the width and breadth of fluorescence imaging. And AI-aided fluorescent imaging has gained a revolutionary development in the last decade for oncologists to perform high efficiency analysis [203–207].

Recently, researches on fluorescence image processing using AI are rapidly growing. Combalia et al. [192] has developed an AI-driven ex vivo confocal microscopy (XVM) pathology. XVM is a high-resolved pathological image instrument which can image freshly resected specimens. One of the objectives of ex vivo microscopy imaging is to acquire visualization of a general tissue morphology that is similar to microscopic histology on the surface of a newly excised specimen. They also designed a Cycle Consistency Generative Adversarial Network (CycleGAN) to perform a style transformation which is consistent with standard H&E style. Another program was designed to perform a diagnosis of basal cell carcinoma. Specifically, they deployed the U-net AI architecture to perform XVM image segmentation and diagnosis. The U-Net

model is an artificial neural network model that consists of numerous convolution/pooling layers serving as encoders. The encoders automatically learn the pattern of images (feature map) without manual parameters selection. U-Net also contains deconvolutional/upsampling layers that serve as decoders [199]. The decoders are able to restore image size and provide pixel-wise classification, that is, the segmentation of the image according to the learned feature map. Further, U-Net and CycleGAN are capable of integration in nature. Unlike original GAN, CycleGAN is that it does not require a paired sample for training [202]. The paired sample usually implies how transformation is performed within the same object. In the XVM case, only XVM images sample are required for training. The XVM image after GAN transformation is highly similar to conventional pathology and thus much more explainable. This is what is called digital staining. The U-Net diagnosis model also demonstrates a high balanced accuracy (0.887 +/−0.05).

In addition to utmost augmenting fluorescent image segmentation by supervised learning, unsupervised algorithm also shined. Lu et al. [196] has developed a self-supervised CNN cluster for fluorescence microscopy images. Unlike conventional CNN, the CNN cluster is able to learn the pattern of single-cell level feature representations. The clusters themselves are proved to be robust. This newly designed pipeline is able to save time and cost of manual labelling. Further, the high-quality feature representations discovered by AI exhibit a profound potential for downstream analysis. The above cases elaborated that AI as a powerful tool for addressing the challenges and broadening the advancement of fluorescence imaging techniques. There are other applications that focus on object detecting, artificial labelling or image restoration, too [208].

4.7. Molecular imaging

As aforementioned, conventional light field microscopy have a limit on its resolution scale of about half of the light wavelength [193,194]. It's been proved that a disrupted genome can reveal the structural change of its cell nucleus. However, molecular-level diagnosis requires an imaging tool with higher magnification [209]. The super-resolved microscopy (SRM) has increased the resolution scale about twenty times higher than light field microscopy, especially the AI-aided molecular imaging, exhibiting the potential to resolve this challenge. AI approaches combined with molecular imaging can have considerable impact on cancer outcomes through improved detection and diagnosis [210]. There are three types of SRM in the mainstream. Three types of SRM are stimulated emission depletion (STED) microscopy, structured illumination microscopy (SIM), stochastic optical reconstruction microscopy (STORM)/photoactivation localization microscopy (PALM) and super-resolution structured illumination microscopy (SR-SIM). Simulated emission depletion (STED) uses a technique called spatially patterned excitation that can lower the point spread function when two lasers are used together in the focal plane. Stochastic optical reconstruction microscopy (STORM) is part of the single-molecule localization (SMLM) family. It can only excite a single fluorophore with photoactivatable properties. Such a strategy can reduce spatial overlap and thus can increase the resolution. Specifically, the random activation makes a single fluorophore "on and off" repetitively. Next, a construction process is necessary to position the location of the single fluorophore. This technique makes fluorescence microscopy's resolution scale as large as 5 nm. Combining AI with this state-of-art technique would be even fewer due to few limitations. Phototoxicity, bleaching and low time resolution are significant limitations of the application of long-time in vivo imaging. The current application of AI in SRM mainly focuses on promoting signal-to-noise ratio (SNR) and resolution.

Through a complex network architecture that combines wide-field and SMLM data as input, AI models can directly map sparse SMLM data from microtubules, mitochondria or nuclear pores directly to their SRM output images. The DL attached STORM provided a better solution for image reconstruction, especially when confronting the low SNR and high emitter density situation [197]. It was also much faster. This method is suitable for blinking datasets and does not require prior information about ground floor shape. The other application of AI in SRM technology is to address the problem of anisotropy. In light-sheet microscopy imaging, axial resolution is typically 2–3 times worse than lateral resolution. Park et al. have announced that their technique could improve the anisotropic point spread function (PSF) by utilizing a cycle-consistent generative adversarial network(cycle-GAN) [198]. Usually, it was challenging to achieve isotropy. Because no manual fine-tuning of parameters is required, DL offers advantages in capturing the statistical complexity of image mapping and enabling end-to-end image transformation. Another application of AI in SRM technology is to improve the autofocus system. Lightley et al. [195] have proposed a long-range optical auto-focus system utilizing a CNN. The new technique solved problems brought by mechanical drifting of the microscopic components and outpaced the traditional non-AI autofocus technique. The AI-aided autofocus has been tested in daily tasks for three months and showed robustness in daily operations. The community increasingly recognizes the potential of AIinmolecular imaging. For instance, the application of molecular classification has revolutionized the way brain tumors are managed, leading to enhanced prognostic accuracy and personalized treatment options. Todd Hollon et al. developed a rapid AI-based diagnostic screening system called DeepGlioma to streamline the molecular diagnosis of diffuse gliomas, achieving a mean molecular classification accuracy of $93.3 \pm 1.6\%$ [211]. Besides, cancer is a disease that comes with profound heterogeneity, and the single-molecule localization property can be a promising solution for this challenge. More studies may swarm into this field in the near future.

5. Conclusion and perspectives

As shown in the overview of AI-assisted optical imaging for cancer theranostics (Fig. 8), despite major advancements in cancer management and treatment, cancer remains the world's primary cause of death. Early detection and diagnosis increase the likelihood of survival significantly when cancers are small and localized. However, the sensitivity and specificity needed for detecting cancer at the asymptomatic or very early stages are not present in current approaches for detection and diagnosis. For better illness management and patient outcomes, it is necessary to create faster, more dependable technologies that can detect disease early. Optical imaging is a quick, non-destructive analytical technique that can give very exact details on the molecular make-up and biological makeup of samples. Adopting AI for cancer detection has benefits and drawbacks, just like AI therapies. AI in diagnosis is capable of defining tumors, categorizing cancers, predicting clinical efficacy, and other tasks. AI can automate data and information about tumors to help clinicians with their diagnosis and treatment through DL. The field of tumor diagnosis and treatment will benefit greatly from the integration of AI with medical imaging. AI has the potential to accelerate and standardize diagnosis but also to increase overdiagnosis. The issue with the gold standard cannot be resolved by machine learning, but it can be made worse by it. The question of whether a cancer diagnosis is related to life expectancy or quality of life is ultimately important for patients and medical professionals. Before these methods are extensively used, we feel that the prospect of teaching machine learning algorithms to identify categories that fall between "neoplastic" and "non-neoplastic" should be carefully considered.

Yet data collection and sharing that affected patients' rights and privacy led to inconsistencies in the usage of medical AI. Doctors and patient organizations in the area have expressed outrage over hospitals selling patient data alone. It is challenging for regulatory bodies to control the sophistication of AI algorithms. The AI system is more likely to result in iatrogenic dangers than a single doctor's misdiagnosis would harm people. Consequently, there is a larger requirement for systematic debugging, auditing, comprehensive simulation and validation, and prospective evaluation when AI algorithms are used in clinical practice.

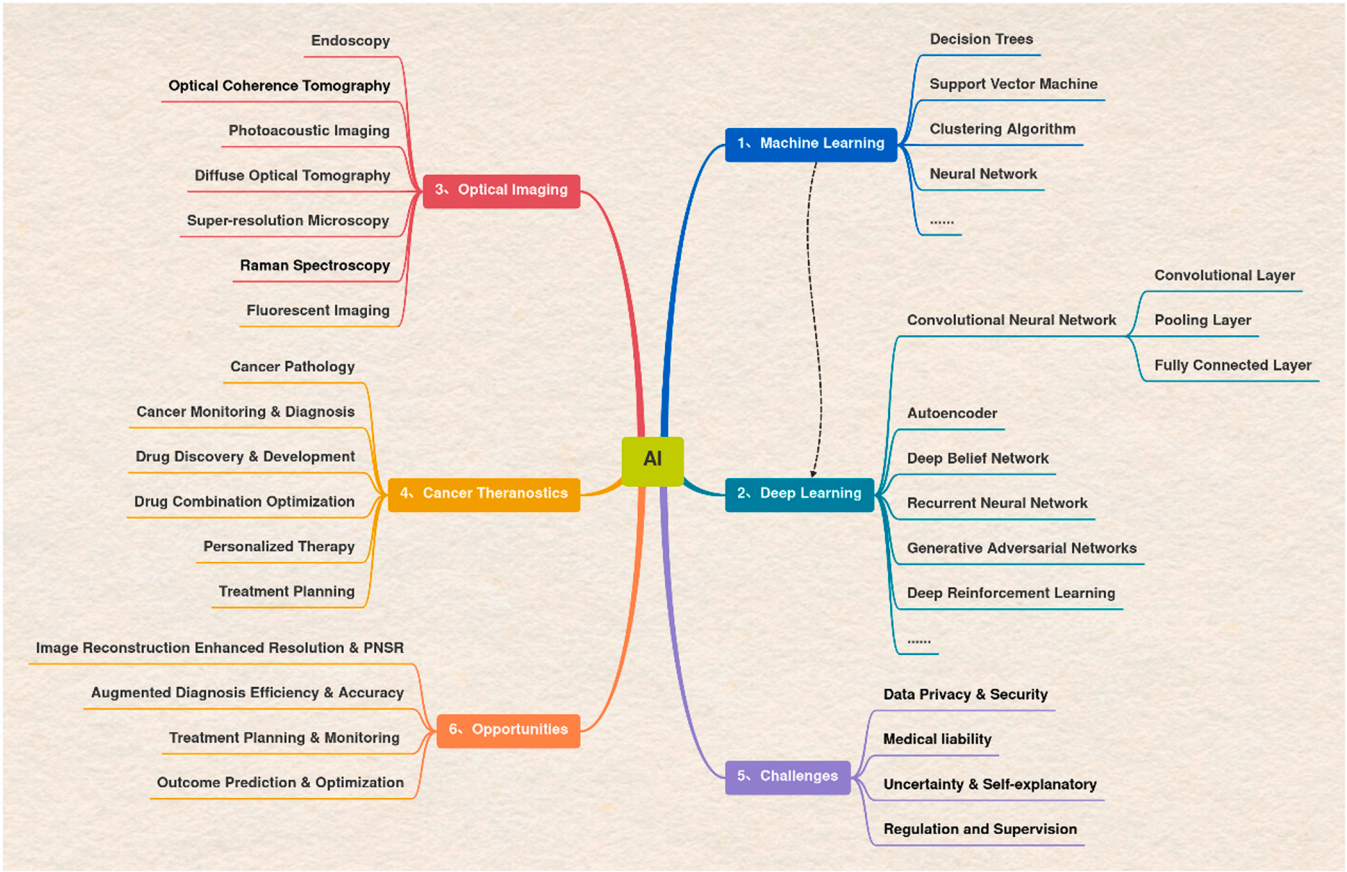

Fig. 8. Summary of this review on artificial intelligence (AI) aided optical imaging for cancer theranostics.

In order for these AI firms to fulfill or even exceed the regulatory criteria of the regulatory authorities, they truly need to increase their needs and produce more evidence and trustworthy verification.

The integration of several levels of data and thoughtful decision-making are essential components of medical decision-making. In the specialized field of oncology, there are numerous elements to take into account while making medical decisions. Even with ongoing technological advancements, accurate tumor diagnosis, qualitative tumor analysis, and tumor monitoring remain difficult tasks. While AI has made significant strides in tumor imaging, there are still obstacles to be cleared before it can be employed extensively in the clinic. The amount of research on machine learning for medical pictures is astounding. But this expansion does not necessarily result in improved clinical outcomes. The increased research output might be driven more by academic incentives than by physicians' and patients' requirements.

Because there is now a dearth of extensive data, most artificial intelligence systems are currently inaccurate and can only be used to treat a small number of common ailments. It is not difficult to find that in the aforementioned study, the accuracy increased with the number of training samples employed. But data standardization and privacy laws have made it difficult to acquire and share data. In parallel to quantity, data quality is also crucial, particularly for medical data, which calls for qualified specialists to manually provide "standard answers" in order to increase AI accuracy, but this may be a time- and resource-consuming procedure. Even if AI's accuracy is compelling enough, it will still be difficult to understand its behavior. Even while DL algorithms produce the intended outcomes, it can be challenging to comprehend how computers "think" in order to do so because they are so sophisticated. But there are more solutions than issues. Since there is a dearth of both quantity and quality of data, more and more public standard databases, like The Cancer Imaging Archive, have been built. As a result, researchers now have more trustworthy optical imaging data available for free use. Unsupervised learning-aided optical imaging can be used by researchers to lessen the amount of missing "answer" photos in the data. And the AI-aided optical imaging will further boost the advancements of decreasing the complexity of handling high-dimensional ill-posed inverse issues and the unpredictable nature of the actual imaging physical process, as well as the high-resolution optical image acquisition, reconstruction, early cancer diagnosis, high-efficiency analysis and clinical-decision making, therapy planning and administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. I confirm that this research is original and has not published previously and not under consideration for publication elsewhere, and if acceptable, I will not publish elsewhere in English or in any Language.

Data Availability

Data will be made available on request.

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