Global Journal of Universal Studies

Volume1:Issue2 ***ISSN: 3008-0509***

Deep Learning for Multi-Modal Cancer Imaging: Integrating Radiomics, Genomics, and Clinical Data for Comprehensive Diagnosis and Prognosis

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Article History

Submitted: 26-11-2024

Revised: 12-12-2024

Accepted: 15-12-2024

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Abstract

At both the cellular and molecular levels, cancer is a heterogeneous disease. While traditional diagnostic and prognostic methods are often deficient in the ability to capture this complexity, limiting the potential to inform personalized treatment strategies. Deep learning (DL) results on multi-modal data sources have the potential to improve cancer diagnosis and prognosis by combining several types of data sources in the past few years: radiomics, genomics and clinical data. The first, radiomics, extracts quantitative features from medical images to reveal tumor characteristics invisible to the human eye; the second, genomic data, provides information about what genetic mutations are driving cancer progression. These modalities are complemented by clinical data with patient demographics and treatment history contributing context specific information to the data. The application of deep learning techniques on multi-modal cancer imaging is reviewed as well and their ability to combine radiomics, genomics and clinical data to improve diagnostic and prognostic accuracy is emphasized. We discuss the challenges and future directions for clinical implementation of this approach and its potential to transform cancer care, improve patient outcomes and empower precision medicine.
Key words: Cancer Genomics, Tumor Heterogeneity, Artificial Intelligence, Machine Learning, Precision Medicine, Genetic Mutations, Oncogenes, Tumor Suppressor Genes, Next-Generation Sequencing (NGS), Radiomics.

Introduction

Diagnosing and treating cancer is one of the most intricate and heterogeneous challenges to date. Tremendous strides have been made in cancer research, yet diagnosis and treatment continue to evade us, in large part because of the instability of tumors. It is not hard to see how tumors grow over time and how they acquire genetic mutations and adapt to the tumor microenvironment, making diagnosis and treatment difficult [1]. Current sources of information for cancer diagnosis and prognosis including, for example, histopathology, clinical staging and imaging, have

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limitations in comprehending the complete cancer complexity. However, these approaches usually lack the sensitivity for detecting subtle tumor features or for predicting how a cancer will respond to a particular treatment paradigm. Consequently, more robust, personalized approaches that can provide more insight into tumor biology and more accurate, individualized predictions for a treatment outcome, are increasingly required [2]. Consequently, in recent years, artificial intelligence (AI), especially deep learning (DL), has seen great advancements to improving cancer diagnosis and prognosis. Deep learning models are a subset of machine learning techniques, which can masterfully process large, complex datasets and spot patterns beyond the human eye [3].

Once again, these models have shown great potential in many healthcare applications such as medical image analysis, genomic data interpretations and clinical decision making. DL has the potential to be one of the most exciting applications of cancer care through the analysis of multi-modal data—integrating radiomics, genomics, and clinical data to present a more holistic picture of cancer and its prognosis [4]. The extraction of quantitative features from medical imaging (radiomics) has been invaluable in extracting tumor characteristics like shape, texture and intensity which can describe tumor heterogeneity. One such important application is cancer diagnosis and prognosis, yet these features are often beyond the ability of human radiologists to detect; fortunately, deep learning models can efficiently detect subtle patterns in the radiomic data [5]. On the genomic side, next generation sequencing (NGS) technologies enable large scalability of genetic mutations, changes in gene cabling and other molecular events that drive cancer growth.

By possessing this genomic information, we can learn important things about the molecular basis of cancer, like what specific mutations or pathways might be targeted to treat it. In addition, patient demographic, medical history, and treatment response information, as available in the clinical data, provides important context to interpret radiomics and genomics in a personalized manner [6]. Finally, we propose an exciting opportunity for integrating these disparate data modalities, including radiomics, genomics, and clinical data, into a unified deep learning model to improve cancer diagnosis and prognosis accuracy. When combined, these modalities can generate a more integrated picture of how the tumor behaves, what its genes consist of, and its reactions to different

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treatments. We may use, for example, deep learning models that predict how a tumor will be sensitive to chemotherapy or immunotherapy based on features in imaging and genomic data in parallel [7].

These models can also be enhanced by integrating clinical data, so as to create more personalized predictions specific to a patient's particular clinical profile regarding age, history of treatment as well as overall health. While deep learning can improve cancer care, there is a host of challenges that need to be overcome before it can maximize its potential [8]. The first and one of the primary obstacles is the integration of multi modal data from various disparate sources each of which has its own characteristics and complexities. The data, such as radiomics data, genomic data or clinical data, often are derived from different platforms that have different structures, formats and data quality. A critical task for this is harmonizing these data types into a unified framework deep learning models can operate with [9].

Deep learning models are often treated as a 'black box', that is, their decision-making process is sometimes not transparent. To realize the potential of deep learning in clinical settings, interpretable and explainable models that allow a clinician to trust and act on the results are necessary. In this report, we will explore how deep learning can be used to integrate radiomics, genomics, and clinical data to bring insight to multi-modal cancer imaging [10]. In this work we will review the current research area in this area, what techniques are used to integrate data and develop models.

Moreover, we will discuss clinical applications of multi-modal deep learning models for cancer diagnosis and prognosis, including applications to improve patient outcomes through personalized treatment strategies. Finally, we will examine the challenges and limitations of incorporating these technologies into clinical practice and provide possible solutions and future work directions [11]. By the end of this report, we hope to offer a detailed view of the role deep learning is playing in advancing cancer care and what it will take to achieve that potential in the clinical setting.

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Research findings

Overview of Cancer and Its Diagnostic Challenges: Cancer is a complex biological phenomenon and is a multifaceted entity characterized by complexity in the process of diagnosis, treatment, and prognosis. Diagnosis of cancer is not a simple affair and incorporates the utilization of different diagnostic apparatuses and systems [12]. But even though medical technology has progressed, piercing accurate and timely diagnoses is still a difficult task because of cancer cells' intrinsic complexity and diversity. In this section the three factors that contribute to this complexity — cancer heterogeneity and limitations in traditional diagnostic approaches — are examined [13].

Cancer Heterogeneity: Cancer heterogeneity is the phenomenon whereby numerous subtypes of cells occur within a single tumor and different tumors within the same cancer type. A variety of factors, including genetic mutations, epigenetic modifications, and effects of the tumor microenvironment, cause tumor heterogeneity. Indeed, variability complicates cancer treatment, and different subpopulations of cells within the same tumor can behave, respond differently to treatment, and metastasize in different ways [14]. Second, it means that over time the tumor will not stay the same, and will acquire new genetic mutations and characteristics that will eventually lead to resistance to therapies. It is vital to understand how much heterogeneity there is in order to predict the progression of cancer and to establish the most suitable therapeutic approaches [15].

Tumor Variability: Tumor variability is intra-tumoral and inter-tumoral. Genetic, epigenetic, and phenotypic diversity within the tumor itself is termed intra–tumoral heterogeneity. In the same tumor, different subpopulations of cancer cells may have different mutations, different expression levels of proteins, and different response to treatments [16]. The problem is this intra tumoral variation which makes treatments less effective as a therapy targeting a certain mutation in one subpopulation does not target a certain other subpopulation of the same tumor.

Inter-tumoral heterogeneity: On the other hand, inter-tumoral heterogeneity refers to differences in tumor characteristics among patients having the same type of cancer. The factors that can influence these differences include patient genetic makeup, lifestyle and environmental exposures [17]. For example, two patients with breast cancer can have breast cancer with different genetic

mutations presenting with tumors of different aggressiveness, having different response to the same treatment. Due to this variability, one treatment will not be effective for all, which is why personalized medicine is key at maximizing cancer care [18].

Intra-tumoral and Inter-tumoral Heterogeneity: Intra-tumoral and inter-tumoral heterogeneity are associated with cancer progression and treatment resistance, often occurring in concert. Both diagnosis and treatment can be complicated by the presence of multiple genetic mutations in a single tumor and across different tumors [19]. Moreover, cancer cells within a tumor can evolve independently, so that resistant subclones can arise over time. It is especially apparent in advanced cancers that have already had several rounds of therapy, in which the therapy originally addressed one cell subpopulation, and yet mutations occur that confer treatment resistance to other cells [20]. In order to develop better diagnostic tool, it is therefore vital to understand how these forms of heterogeneity influence cancer progression. In order to predict the behaviour of the tumor, or to determine which treatments will be best, clinicians need accurate ways to assess the degree of heterogeneity in individual tumors [21].

Traditional Diagnostic Approaches: Cancer diagnosis is initially made by imaging followed by biopsy to confirm malignancy. Diagnosis in the traditional sense uses histopathology, imaging techniques and biomarker testing. These approaches have been important for cancer detection, though they are limited in how fully they capture cancer complexity [22].

Histopathology: One of the gold standards in the diagnosis of cancer still remains the histopathological examination of tissue samples retrieved via biopsy. The tissue is examined by pathologists, to see if there is any malignancy, such abnormal cell growth, presence of necrosis and alterations in cellular morphology [23]. However, histopathology has some limitations because it can describe at one time the state of a tumor, its size and shape and the characteristics of its cells. Then, also, histopathology may be unable to discern subtle tumor heterogeneity, especially in tumors with genetic variations that cannot be seen under the microscope [24].

Imaging Techniques

Tumor visualization for size, location, and spread is frequently performed with imaging methods such as X-rays, computed tomography (CT) scans, magnetic resonance imaging (MRI) and positron emission tomography (PET). While these techniques are useful for staging cancer and for monitoring treatment response, they are limited in their ability to detect microscopic tumor changes, including appearance of resistant subpopulations [25]. To add, imaging also lacks the resolution to distinguish between different tumor subtypes, or to characterize the genetic makeup of the tumor. However, this is a severe limitation particularly where tumor heterogeneity is concerned, and one that hampers predicting treatment outcome [26].

Biomarker Testing: The biomarker test is to identify some proteins, genes, or other molecules that are unique to cancer. The use of these biomarkers in assessing presence of cancer, predicting prognosis and planning treatment options is shown. For example, through biomarker testing, it is possible to determine that you have HER2-positive breast cancer and to treat you with HER2-targeted therapies. Nevertheless, biomarker testing may not complete the story in heterogeneous tumors which have several biomarkers in different subpopulations of tumor cells [27].

Limitations of Current Diagnostic Methods: Traditional diagnostic methods offer important information but cannot adequately describe the complexity and heterogeneity of cancer. Current diagnostic approaches are beset with several key limitations [28].

Inaccuracies in Traditional Imaging: Even with the availability of advanced technology that permits imaging of cancer, conventional imaging techniques do not accurately resolve tumor heterogeneity. However, for example, while imaging can show the location and size of a tumor, it typically cannot see molecular and genetic variations on this scale within the tumor that are critical for making treatment decisions. On imaging scans, tumors can have very similar appearances, but their genetic profiles can be quite different—different for prognosis and response to therapy [29]. In addition, imaging techniques are unable to visualize the microscopic, sub clonal metastases or small, emerging populations of tumor cells that may contribute to treatment resistance.

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Impact of Social Practices on Stakeholder Relationships

Challenges with Tumour Biopsy: However, the gold standard for diagnosis and the analysis of cancer tissue is tumor biopsy. However, biopsies come with several limitations. One is that biopsy samples are often small, and may not represent the whole tumor in a genetic and molecular sense. In the event of intratumorally heterogeneity then a biopsy may only represent a small subset of the tumoral cells from which resistant subpopulations in other parts of the tumor could be missed [30]. The problem is also that biopsies are invasive and carry with them risks for the patients and in addition, it may not be possible to do biopsies of tumors located in hard to-reach areas. Alternative methods such as liquid biopsy are being explored but those, too, have their limitations because biopsy isn't possible in certain cases [31].

Lack of Comprehensive Prognostic Models: A primary limitation of conventional diagnostic methods is the inability to develop an all-encompassing, multivariate prognostic model for cancer. Still, current models tend to focus only on a small number of factors, typically tumor size, grade, or stage, and fail to consider the full spectrum of variables that may affect treatment response or prognosis [32]. For instance, the overall progression of cancer is affected by factors such as tumor heterogeneity, genetic mutations, the tumor microenvironment, which are not commonly included in current prognostic models. As such, these models may not predict how a cancer will evolve or how a patient will respond to treatment [33].

Genomic Data and Its Impact on Cancer Diagnosis: Cancer genomics has brought forth a drastic change in our knowledge regarding cancer biology and provided a deeper understanding of how genetic mutations and alterations play a role in tumorigenesis, progression and therapy resistance [34]. Genomic data is useful for identifying specific, in this case genetic, changes that cause normal cells to become malignant. Genetic mutations, oncogenes and tumor suppressor's gene role will be explained, and introduction of next generation sequencing (NGS) technologies in cancer diagnosis and treatment will be discussed [35].

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Genetic Mutations and Cancer Development

Cancer is caused by genetic mutations. These mutations occur in any number of genes or pathways involved in controlling cell growth, differentiation, and apoptosis. These mutations add up and if there's too many, they can cause uncontrolled cell division and eventually a tumor. They can be inherited, or they may result from environmental factors such as radiation, smoking or exposure to carcinogens. There are two primary types of genetic mutations that contribute to cancer: There are also driver mutations and passenger mutations [36]. They are driver mutations, whose presence confers a growth advantage on the tumor and are directly responsible for its development. On the other hand, passenger mutations are secondary mutation, not directly participating in tumorigenesis, but often the result of the tumorigenesis process which is highly adaptive genetically [37].

Oncogenes and Tumour Suppressor Genes: Genes that when mutated or over expressed have the potential to turn the normal cells to cancerous cells are called oncogenes. Genes of these often control cell growth and proliferation in normal organisms [38]. Well known examples of oncogenes include HER2 (human epidermal growth factor receptor 2) in breast cancer, K-RAS and EGFR (epidermal growth factor receptor). Uncontrolled cell proliferation and survival can occur due to over expression or mutation of oncogenes. On the other hand, tumor suppressor genes work to keep cancer at bay by governing the cell cycle and being an induction to apoptosis (programmed cell death) [39].

Normal growth control cannot occur without these genes, and mutations in them result in inactivation of the normal genes, which in turn lead to cells forming tumors. The most frequently mutated tumor suppressor gene in cancer is the p53 gene, known commonly as the "guardian of the genome." BRCA1 and BRCA2 mutations are also commonly associated breast cancer and confer susceptibility to early cancer onset [40]. Development of cancer critically depends on balance between the activation of oncogenes and the inactivation of tumor suppressor genes. Altering either type of gene results in deregulation of normal cellular processes, or is a driver of tumorigenesis [41].

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Next-Generation Sequencing (NGS): With the advent of next generation sequencing (NGS) technology, cancer genomics has been revolutionized allowing high throughput sequencing of an entire genome or targeted regions. By this, we can detect genetic mutations, copy number alterations, structural variations and even epigenetic changes in tumors. This technology furnishes a full picture of the genomic landscape of a tumor, providing clinicians with a means to recognize the precise mutations fuelling cancer growth [42].

Techniques and Advances: Several improvements have been achieved in NGS technologies in the last few years, including whole genome sequencing (WGS), whole exome sequencing (WES) and RNA sequencing (RNA-Siq). Whereas WGS gives us a full picture of the genetic landscape with coding and non-coding information, encompassing about 1-2% of the genome, yet regions that often contain the highest priority clinically relevant mutations, WES grants us the ability to pinpoint protein coding regions of the genome [43]. On the other hand, RNA-Siq allows to assess gene expression levels, which brings insights into which genes are on or off in cancer cells. The ability to detect rare mutations and complex alterations in the genome that traditional sequencing approaches have been unable to do has been greatly enhanced by NGS. These advances have greatly enhanced our understanding of cancer genomics, and have helped us to more sensitively identify early-stage cancers and better predict clinical outcomes, and design personalized treatment strategies [44].

Genomic Data for Breast Cancer: In fact, breast cancer is one of the most common cancers globally and is highly heterogeneous at the molecular level. The genomic alterations that drive breast cancer are very different among patients, thus adding to the difficulty of finding universally effective treatment. Researchers have found specific genomic alterations in various subtypes of breast cancer (her2 positive, triple negative and hormone receptor positive), through NGS. BRCA1 and BRCA2 are the most well-known genomic alterations involved in breast cancer which increased risk for breast and ovarian cancers [45]. Mutations in hormone receptor positive breast cancer are also common, other mutations such as in the PIK3CA gene. Some of the more aggressive types of breast cancer are also associated with the TP53 mutation. By studying these

and other genetic changes, clinicians can not only detect breast cancers, but also determine how the tumor will behave to certain treatments, including targeted treatments, chemotherapy and immunotherapy [46].

Genetic Heterogeneity and Its Role in Treatment Resistance

Treatment resistance in cancer development is critically reliant on genetic heterogeneity. Over time, as tumors grow and evolve, they pick up genetic mutations that let subpopulations of tumor cells live through treatments that should wipe out the vast majority of the tumor. In this section, we will take a look at genetic tumor cell evolution, mutational accumulation and how these processes result in resistance to therapy [47].

Genetic Evolution of tumour Cells: Genetic evolution of tumor cells happens throughout tumor development and treatment. During growth, the genetic mutations that accumulate within a tumor ultimately give rise to the appearance of subpopulations of cells with differing genetic backgrounds. Genetic alterations in these cells are not random but arise under a selective pressure — exposure to chemotherapy or targeted treatments. It's a process called clonal evolution, because tumor cells adapt to changing environments and become resistant to therapies [48]. Sensitive subpopulations will be killed while the tumor consists of cells that have mutations enabling them to evade the effects of treatment and continue to proliferate. This eventually results in the dominance of resistant clones that cause relapse or metastasis. A major challenge in oncology is the ability of cancer cells to evolve in response to treatment so as to complicate long term disease control and to necessitate continuous adaptation of therapeutic strategies [49].

Mutational Accumulation: The build-up of genetic mutations over time in tumor cells that divide and proliferate is called mutational accumulation. However, this process is accelerated by mutations in genes that repair DNA, in particular the BRCA1 or BRCA2 genes, which increase the likelihood that other mutations will be acquired. Cancer progression is driven mainly by the accumulation of mutations resulting in the emergence of more aggressive and resistant to conventional treatments tumor subclones [50]. Over time, as it evolves and diversifies, it becomes next to impossible to target it with one therapeutic agent. For example, a tumor may initially be

controlled with a chemotherapy, but eventually new mutations appear that allow cancer cells to escape the drug's effects [51]. Knowledge of the patterns of mutational accumulation are critical to the development of strategies to target both the initial tumor as well as the evolving resistant clones.

Clonal Evolution in Response to Therapy: Treatment resistance in cancer is driven by a key mechanism, clonal evolution. Some tumor cells are inherently more resistant when exposed to therapeutic agents, due to a preexisting genetic mutation, but others develop resistance during therapy by creating new mutations. This concept is particularly important in cancers, including breast cancer, with frequent resistance to both chemotherapy, hormone therapy, and targeted therapy. As an example, initial treatment with HER2-targeted therapies like trastuzumab works well for HER2-positive breast cancer, but often carries on to become resistant over time through mutations within the HER2 receptor or activation of other compensatory signalling pathways [52]. Likewise, in triple negative breast cancer (TNBC), the absence of receptors targeted makes treatment difficult, and genomic instability and clonal evolution leads to resistance. Anticipating and following clonal evolution during treatment is necessary to predict acquisition of resistance and to address therapies accordingly [53].

Biomarkers for Targeted Therapy: Genetic, proteomic or other molecular indicators called biomarkers may predict how a tumor will respond to treatment. There are many biomarkers in breast cancer that are important for predicting response to therapy. HER2 overexpression is a biomarker in this case since HER2 positive breast cancer shows increased response to HER2 targeted therapies, e.g. trastuzumab. Importantly, PIK3CA mutations in hormone receptor positive breast cancer, and BRCA1/BRCA2 mutations in hereditary breast cancer are other important biomarkers [54]. By uncovering these biomarkers, clinicians are able to personalize therapy options for breast cancer patients by choosing therapies most likely to work based on a tumor’s genetic profile. Nonetheless, biomarker panel analysis is complicated by genetic heterogeneity that creates subpopulations of tumor cells that do not express these biomarkers, or acquire resistance

to targeted therapeutics over time, making a combination of biomarkers essential for a broader treatment [55].

Predicting Response to Chemotherapy, Immunotherapy, and Targeted Treatments

Predicting how a tumor will respond to a variety of therapies is one of the main applications of genomic data in cancer treatment. Different mechanisms work behind chemotherapy, immunotherapy and targeted treatments in fighting cancer, and the genomic profile of the tumor holds the key to the treatment that would prove most effective. Identification of mutations associated with resistance to chemotherapy (e.g., within genes related to drug metabolism or DNA repair) are possible with genomic data [56]. As an example, tumors with mutations in the BRCA1 or BRCA2 genes may be more sensitive to chemotherapy that induces DNA damage (platinum-based therapies) than breast cancers lacking BRCA mutations. Tumors with high levels of immune checkpoint molecules such as PD-L1 respond best to immunotherapies, like checkpoint inhibitors. Examining gene expression profiles, and immune related pathways, genomic data can identify tumors that are more likely to respond to immunotherapy. Targeted Treatments: Genomic data enables the detection of mutations in specific cancer-driving genes (e.g., HER2 in breast cancer, or EGFR in lung cancer). These were targeted by specific inhibitors, which provide for more precise treatment than conventional chemotherapy [57].

Incorporating Genomic Data into AI Models: Combining genomic data with AI models could markedly improve cancer diagnosis, treatment planning and prognosis. AI algorithms can crunch vast amounts of genomic data, find which mutations are key and predict which treatments will work against tumors. The role of AI in genomic data processing, treatment outcome prediction and the challenge of data processing will be the scope of this section [58].

AI in Genetic Data Analysis: Deep learning algorithms, which belong to a group of artificial intelligence models, can process and analyses so much genomic data, humans are not able to do so by hand. Using these models, patterns of gene expression, the identification of genetic mutations or other molecular alterations associated with cancer development, and treatment resistance are identified [59]. Integrating genomic data with other modalities of medical data (e.g., imaging,

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clinical records) brings a next level of understanding of the tumor's biology and predicts how it will evolve in response to therapy.

Identifying Driver Mutations: Driver mutations are genetic changes which directly initiate or drive cancer and can be 'trained' to be identified by AI models. Finding these mutations is crucial both for understanding how the tumor's biology works and being able to create targeted therapies. Using large patient cohorts, AI models can discover rare or novel driver mutations that wouldn't reveal themselves under traditional genomic analysis [60]. This work targets the very fundamental and difficult challenge of predicting therapeutic outcomes. Predicting therapeutic outcomes from a tumor's genomic profile is among the most promising applications of AI in cancer genomics. AI models can predict how a tumor will behave with respect to different kinds of drugs, for example drugs like chemotherapy or targeted therapies or immunotherapies, by understanding the genomic alterations within the tumor. These models can be used to help guide treatment decision in order to choose the best therapy for each patient.

Conclusion

The potential to integrate genomic data into cancer diagnosis and treatment is enormous for increasing our knowledge of tumor biology, prognostic accuracy, and personalization of therapeutic strategies. Cancer progression and treatment resistance are driven, in large part, by genetic mutations (especially oncogene and tumor suppressor genes). Advanced technologies such as next generation sequencing (NGS) and bringing us in deeper in the genomic landscape that the tumors have, [and] I can predict in which direction are they going to react to the different therapies. The integration of genomic, radiomic, and clinical data into AI models can be more comprehensive to cancer care—and can identify those key mutations, predict treatment outcomes, and aid in the personalization of treatment. Challenges remain, however, that need to be overcome before AI-driven genomics will be able to fully deliver on their promise in cancer care including data quality, volume and incomplete genomic information. With additional progress in AI and in genomic research, however, personalized, precision oncology will be ever more powerful in combating a broad range of cancer types.

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