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Self-Supervised Learning for Multimodal Precision Oncology: Unlocking Unlabeled Clinical and Imaging Data

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ABSTRACT

Cancer remains one of the leading causes of morbidity and mortality worldwide despite remarkable advances in molecular diagnostics, targeted therapeutics, immunotherapy, and precision medicine. Modern oncology continuously generates enormous quantities of heterogeneous biomedical data through radiological imaging, digital pathology, genomic sequencing, transcriptomics, proteomics, metabolomics, laboratory investigations, electronic health records, wearable technologies, and longitudinal clinical documentation. Although these datasets possess tremendous potential for advancing precision oncology, only a small proportion is manually annotated, creating a major limitation for conventional supervised artificial intelligence (AI). Self-supervised learning (SSL) has emerged as a transformative machine learning paradigm that enables models to learn generalized biomedical representations directly from unlabeled data without requiring extensive manual annotation. By leveraging pretext tasks, contrastive learning, masked modeling, multimodal representation learning, transformer architectures, graph neural networks, and foundation models, SSL has significantly improved computational oncology across medical imaging, digital pathology, radiogenomics, computational pathology, multi-omics integration, clinical decision support, and personalized therapeutics. Furthermore, SSL facilitates transfer learning, few-shot learning, multimodal foundation models, digital twins, and agentic AI, thereby accelerating development of generalized biomedical intelligence for precision medicine. Despite remarkable advances, important challenges remain regarding multimodal data harmonization, computational scalability, interpretability, regulatory validation, and clinical translation. This review provides a comprehensive overview of self-supervised learning in multimodal precision oncology, highlighting computational foundations, current applications, implementation challenges, and future perspectives for unlocking the full potential of unlabeled biomedical data.[1]

Keywords: Self-supervised learning, Precision oncology, Artificial intelligence, Multimodal learning, Medical imaging, Digital pathology, Foundation models, Computational oncology, Multi-omics, Personalized medicine.

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1.Introduction

Cancer is a biologically heterogeneous disease characterized by genomic instability, epigenetic regulation, immune diversity, metabolic reprogramming, and continuous interactions between malignant cells and the tumor microenvironment. Although advances in molecular medicine have substantially improved diagnosis

and treatment, individualized patient management remains challenging because cancer biology extends beyond isolated molecular alterations into highly complex multimodal biological systems.[2]

Modern oncology generates unprecedented quantities of biomedical information through computed tomography, magnetic resonance imaging, positron emission tomography, mammography, digital pathology, genomic sequencing, transcriptomics, proteomics, metabolomics, laboratory biomarkers, wearable biosensors, and electronic health records. While these multimodal datasets provide comprehensive descriptions of tumor biology, only a small proportion has been manually annotated because expert labeling requires considerable time, cost, and specialized clinical expertise.[3]

Conventional supervised artificial intelligence relies heavily on labeled datasets for training predictive models, thereby limiting scalability across diverse healthcare environments. Self-supervised learning addresses this limitation by enabling artificial intelligence to learn generalized biomedical representations directly from large collections of unlabeled data through automatically generated learning objectives.[4]

The emergence of self-supervised learning therefore represents a major paradigm shift in computational oncology by unlocking previously inaccessible biomedical information while enabling generalized artificial intelligence capable of supporting precision medicine across multiple cancer domains.[5]

2.Evolution of Self-Supervised Learning

Artificial intelligence within oncology initially depended upon supervised learning approaches that required manually annotated imaging studies, pathology slides, genomic datasets, and clinical records. Although these methods achieved impressive predictive performance, acquisition of expert annotations remained expensive, labor-intensive, and often impractical for large biomedical datasets.[6]

Unsupervised learning subsequently enabled discovery of hidden biological patterns without manual labeling; however, these models frequently demonstrated limited performance on downstream clinical tasks because they lacked biologically meaningful representations.

Self-supervised learning emerged as an intermediate paradigm combining the strengths of supervised and unsupervised learning. Rather than requiring external labels, SSL generates supervisory signals directly from the intrinsic structure of biomedical data through pretext tasks including image reconstruction, masked prediction, contrastive learning, temporal ordering, and multimodal alignment.[7]

Recent advances in transformer architectures, multimodal foundation models, graph neural networks, and contrastive representation learning have substantially accelerated self-supervised learning across computational oncology, enabling generalized biomedical intelligence trained using massive unlabeled datasets.[8]

3.Principles of Self-Supervised Learning

Self-supervised learning enables artificial intelligence to acquire meaningful representations without requiring manually labeled datasets. Instead of learning from externally provided diagnostic labels, SSL creates surrogate learning objectives directly from the data itself, allowing models to discover latent biological structure through prediction of missing or transformed information.[9]

Common self-supervised strategies include contrastive learning, masked image modeling, masked language modeling, image reconstruction, predictive coding, temporal sequence prediction, cross-modal alignment, and representation consistency learning. These approaches encourage neural networks to learn generalized features that remain transferable across multiple downstream biomedical tasks.Following pretraining, learned representations can be efficiently adapted through transfer learning, few-shot learning, or fine-tuning using

relatively small annotated datasets, thereby substantially reducing dependence on expensive expert annotation while improving generalizability across healthcare institutions.[10]

4.Computational Architecture of SSL Models

Modern self-supervised learning systems consist of multiple computational layers responsible for multimodal data acquisition, self-supervised pretraining, representation learning, downstream adaptation, and clinical prediction.[11]

The data acquisition layer integrates radiological imaging, digital pathology, genomic sequencing, transcriptomics, proteomics, metabolomics, laboratory investigations, wearable biosensors, medication history, and longitudinal clinical records. Advanced preprocessing pipelines normalize imaging studies, harmonize molecular datasets, encode clinical narratives using natural language processing, and align heterogeneous biomedical modalities.

Transformer architectures, convolutional neural networks, graph neural networks, and multimodal encoders subsequently learn generalized biomedical embeddings through self-supervised pretext tasks. These learned representations are later adapted for specialized oncology applications including diagnosis, prognostic prediction, biomarker discovery, treatment optimization, digital pathology, radiomics, and precision medicine.

Continuous learning from expanding biomedical datasets enables SSL models to improve progressively while maintaining scalability across diverse clinical environments.[12]

5.Contrastive Learning in Medical Imaging

Contrastive learning has become one of the most successful self-supervised learning approaches for medical imaging. Rather than predicting diagnostic labels, contrastive learning trains artificial intelligence to distinguish similar and dissimilar biomedical representations through comparison of different augmented views of the same underlying image.[13]

Radiological imaging datasets derived from computed tomography, magnetic resonance imaging, positron emission tomography, mammography, ultrasound, and hybrid imaging provide ideal environments for contrastive representation learning because millions of unlabeled examinations are routinely generated during clinical practice.

Foundation models pretrained through contrastive learning acquire generalized anatomical and pathological knowledge that subsequently improves tumor detection, lesion segmentation, disease classification, radiomics, treatment response assessment, and longitudinal monitoring while requiring minimal manually labeled data.[14]

6.Self-Supervised Learning in Digital Pathology

Digital pathology has become one of the largest beneficiaries of self-supervised learning because whole-slide imaging generates enormous repositories of unlabeled histopathological images. Artificial intelligence analyzes millions of microscopic tissue regions while learning generalized histomorphological representations through self-supervised pretraining.[15]

Transformer architectures and masked image modeling enable pathology foundation models to infer missing tissue regions, predict spatial relationships, reconstruct histological structures, and learn biologically meaningful tissue representations without manual annotation.

These generalized computational embeddings substantially improve downstream tasks including tumor classification, grading, lymph node metastasis prediction, biomarker discovery, molecular subtype

classification, recurrence estimation, and survival prediction while reducing dependence on expert pathology annotations.[16]

7.Self-Supervised Learning for Multi-Omics

Multi-omics datasets—including genomics, transcriptomics, proteomics, metabolomics, epigenomics, lipidomics, immunomics, and single-cell sequencing—provide comprehensive characterization of cancer biology but frequently lack large manually annotated training datasets.[17]

Self-supervised learning enables transformer architectures and graph neural networks to learn generalized molecular representations directly from unlabeled biological data by predicting masked genes, reconstructing molecular pathways, aligning multimodal biological representations, and modeling biological interaction networks.

These generalized molecular embeddings support biomarker discovery, molecular subtype classification, therapeutic prediction, systems biology research, drug response estimation, and precision medicine while substantially improving transferability across diverse cancer types and biomedical datasets.[18]

8.Multimodal Representation Learning

The greatest strength of self-supervised learning lies in its ability to integrate heterogeneous biomedical information into unified computational representations. Multimodal SSL simultaneously learns from radiological imaging, digital pathology, genomics, transcriptomics, proteomics, laboratory biomarkers, wearable technologies, electronic health records, and longitudinal clinical documentation.[19]

Transformer-based multimodal encoders align diverse biomedical modalities through shared representation spaces while preserving complementary biological information. These unified patient embeddings improve diagnosis, prognostic prediction, therapeutic optimization, toxicity estimation, disease monitoring, and personalized clinical decision-making.

By leveraging vast quantities of unlabeled multimodal biomedical data, self-supervised learning enables increasingly comprehensive precision oncology while reducing dependence on expensive expert annotation and improving generalizability across healthcare systems.[20]

9.AI-Driven Radiopathomics in Precision Cancer Diagnosis

One of the greatest clinical strengths of radiopathomics lies in its ability to improve diagnostic precision through simultaneous analysis of radiological imaging and histopathological information. Artificial intelligence integrates radiomic features, histomorphological characteristics, molecular biomarkers, laboratory investigations, and longitudinal clinical information to generate comprehensive patient-specific diagnostic representations.[22]

Deep learning algorithms combine imaging-derived biomarkers describing tumor morphology, vascularity, texture, heterogeneity, and metabolic activity with microscopic pathological features including cellular architecture, stromal remodeling, mitotic activity, necrosis, immune infiltration, and lymphovascular invasion.

These integrated computational models improve tumor classification, disease staging, molecular subtype identification, recurrence risk estimation, and diagnostic reproducibility while supporting multidisciplinary clinical decision-making across diverse cancer types.

10.Personalized Therapeutics and Treatment Optimization

Radiopathomics provides an increasingly comprehensive biological understanding that supports individualized therapeutic planning. Artificial intelligence integrates radiological imaging, computational pathology, genomic sequencing, transcriptomics, laboratory biomarkers, medication history, and clinical characteristics to predict therapeutic response across multiple treatment modalities.[23]

Machine learning estimates recurrence probability, progression-free survival, overall survival, treatment-related toxicity, and mechanisms of therapeutic resistance while evaluating chemotherapy, targeted therapy, endocrine therapy, immunotherapy, radiation therapy, surgical intervention, and multimodal treatment combinations.

Continuous incorporation of updated imaging and pathological information enables adaptive treatment recommendations that evolve alongside changes in tumor biology, thereby supporting truly personalized precision oncology.

11.Radiopathomics in Immunotherapy

The tumor microenvironment plays a fundamental role in determining responsiveness to immunotherapy. Radiopathomics enables comprehensive characterization of immune-related biological processes by integrating imaging biomarkers with microscopic evaluation of immune-cell infiltration, stromal architecture, angiogenesis, and inflammatory signaling pathways.[24]

Artificial intelligence analyzes tumor-infiltrating lymphocytes, PD-L1 expression, immune checkpoint activity, vascular remodeling, cytokine signaling, and spatial cellular organization together with radiological phenotypes to estimate responsiveness to immune checkpoint inhibitors, CAR-T cell therapies, cancer vaccines, bispecific antibodies, and adoptive cellular therapies.

These multimodal computational representations improve patient selection while supporting increasingly individualized immunotherapeutic strategies based on the biological characteristics of each patient's tumor microenvironment.

12.Drug Discovery and Clinical Decision Support

Artificial intelligence-driven radiopathomics is increasingly contributing to oncology drug discovery through integration of radiological imaging, pathology, molecular biology, pharmacology, and clinical outcome data. Machine learning identifies imaging and histopathological biomarkers associated with therapeutic sensitivity, drug resistance, toxicity, and novel therapeutic targets.[25]

Generative artificial intelligence further supports pharmaceutical research by modeling molecular interactions, predicting treatment response, identifying candidate biomarkers, and accelerating development of personalized anticancer therapies.

Within clinical practice, radiopathomic decision-support systems integrate imaging studies, pathology reports, laboratory investigations, genomic sequencing, treatment history, and electronic health records into interactive clinical dashboards that provide individualized diagnostic summaries, therapeutic recommendations, toxicity estimates, recurrence predictions, and survivorship planning while maintaining physician oversight.

13.Explainable Artificial Intelligence and Clinical Translation

Successful implementation of radiopathomics requires transparent computational reasoning that clinicians can understand and verify. Explainable artificial intelligence (XAI) enables interpretation of multimodal predictions through attention visualization, saliency maps, SHAP (Shapley Additive Explanations), feature attribution analysis, and counterfactual explanations that identify both radiological and pathological features contributing to clinical recommendations.[26]

Several important challenges continue to influence clinical translation. Radiological imaging and pathology are acquired using different technologies, resolutions, and workflows, making multimodal harmonization computationally demanding. Additional concerns include algorithmic bias, interoperability limitations, patient privacy, cybersecurity, regulatory approval, and the need for prospective multicenter clinical validation.

Addressing these issues will require standardized computational pipelines, robust quality assurance, secure data governance, multidisciplinary collaboration, and internationally accepted reporting standards.

14. Emerging Innovations and Future Perspectives

Rapid advances in computational oncology continue to expand the capabilities of AI-driven radiopathomics. Multimodal foundation models trained on enormous biomedical datasets are expected to improve cross-modal representation learning while requiring less task-specific retraining.[27]

Digital twins capable of integrating radiological imaging, digital pathology, multi-omics, wearable technologies, laboratory investigations, and longitudinal clinical information may enable individualized simulation of disease progression and therapeutic response throughout the patient's cancer journey.

Additional innovations including federated learning, spatial transcriptomics, single-cell sequencing, liquid biopsy, agentic artificial intelligence, quantum computing, cloud-native healthcare infrastructure, and generative AI are expected to further strengthen radiopathomic ecosystems while improving scalability, privacy preservation, and clinical applicability.

15. Discussion

AI-driven radiopathomics represents one of the most significant advances in computational oncology by integrating macroscopic radiological phenotypes with microscopic histopathological features into unified computational representations of tumor biology. Unlike conventional diagnostic approaches that evaluate imaging and pathology independently, radiopathomics combines complementary biological information to improve diagnosis, molecular characterization, prognostic prediction, therapeutic optimization, immunotherapy selection, and disease monitoring.[28]

Its ability to integrate radiology, pathology, genomics, laboratory biomarkers, and longitudinal clinical information provides unprecedented opportunities for personalized precision medicine while strengthening multidisciplinary collaboration among radiologists, pathologists, oncologists, surgeons, and computational scientists.

Nevertheless, successful implementation requires continued advances in explainable artificial intelligence, multimodal interoperability, computational infrastructure, regulatory validation, cybersecurity, and equitable deployment across diverse healthcare systems.

16.Conclusion

AI-driven radiopathomics is redefining personalized cancer care by integrating radiological imaging, digital pathology, molecular biology, laboratory biomarkers, and longitudinal clinical information into comprehensive computational frameworks capable of supporting precision oncology.[29]

Advances in multimodal learning, transformer architectures, graph neural networks, digital twins, foundation models, federated learning, and generative artificial intelligence are expected to further strengthen these integrated diagnostic ecosystems, enabling increasingly accurate diagnosis, adaptive therapeutics, continuous disease monitoring, and evidence-based clinical decision-making.

Although important scientific, technical, ethical, and regulatory challenges remain, continued interdisciplinary collaboration among radiologists, pathologists, oncologists, biomedical engineers, computer scientists, and healthcare organizations will accelerate responsible clinical translation of radiopathomics, ultimately improving patient outcomes and advancing the future of precision cancer medicine worldwide.[30]

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