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Review

A narrative review of the prediction of immunotherapy efficacy for treating NSCLC: An artificial intelligence perspective

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ABSTRACT

Immunotherapy efficacy in non-small cell lung cancer (NSCLC) remains variable, with traditional biomarkers (programmed death-ligand 1 [PD-L1] and tumor mutational burden) limited by heterogeneity and sensitivity/specificity constraints. This review evaluates the role of artificial intelligence (AI) in advancing predictive biomarkers through the integration of radiomics, pathomics, and multi-omics. We conducted a narrative literature review (PubMed; Web of Science; chictr.org.cn; clinicaltrials.gov, 2012–2025) using keywords spanning NSCLC, immunotherapy, and AI methodologies (radiomics, pathomics, and multi-omics). The inclusion criterion was studies that developed predictive models for immune checkpoint inhibitor outcomes; the exclusion criteria were non-original research and preclinical studies. Emerging evidence highlights AI's transformative role in the prediction of immunotherapy efficacy for treating NSCLC: radiomics quantifies tumor heterogeneity through computed tomography-based PD-L1 and TMB ≥10 mut/Mb biomarkers, while pathomics refines PD-L1 scoring and immune microenvironment classification. Multi-omics integration synergizes imaging, histopathology, and liquid biopsy data with dynamic models by resolving spatial discordance and temporal clonal evolution. However, clinical adoption requires the standardization of peri-tumoral radiomics, validation of delta-feature protocols, and prospective trials to address overfitting risks in small cohorts. AI-driven multi-omics redefines immunotherapy prognostication, but faces interpretability and ethical challenges. Future validation must prioritize prospective multicenter trials, causal biological linking of radiomic features, and federated learning frameworks to ensure equitable clinical implementation.

1. Introduction

Currently, lung cancer stands as the primary cause of cancer-related mortality in men and ranks second in prevalence among women. The classification of lung cancer, as determined through immunohistochemistry (IHC) and light microscopy, categorizes it into two main types: small cell lung cancer and non-small cell lung cancer (NSCLC).[1,2] Surgery and radiotherapy remain the mainstay treatments for early and mid-stage NSCLC. However, a notable challenge is that over one-third of patients are diagnosed at an advanced stage. The landscape of systemic therapy—including chemotherapy, targeted therapy, and immunotherapy—has broadened, thus providing a more diverse range of therapy options. The impact of these therapies on extending the survival of NSCLC patients has garnered increasing attention.[3] In particular, immune checkpoint inhibitors (ICIs)—notably programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) blockers—have revolutionized the current approach to NSCLC treatment. The realm of clinical trials has witnessed exponential growth, delving into their therapeutic responses and assessing adverse events in the context of lung cancer.

Furthermore, the response pattern of immunotherapy differs from that of traditional therapy, thus making the Response Evaluation Criteria in Solid

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Table 1
Summary of the search strategy.

Items	Specification
Date of search	January 21, 2025
Databases and other sources searched	PubMed/Web of Science/chictr.org.cn/clinicaltrials.gov
Search terms used	Non-small cell lung cancer, NSCLC; immunotherapy, immune checkpoint inhibition, anti-PD-L1 therapy, anti-PD-1 therapy, PD-1 inhibitor, PD-1 blockage, neoadjuvant immunotherapy, neoadjuvant chemoimmunotherapy; radiomics, machine learning, deep learning, artificial intelligence, pathomics, multi-omics
Timeframe	2012–2025
Selection process	Wu conducted a literature search and analysis, consulted with all authors, and reached a consensus

Tumors insufficient for objective efficacy assessment. Consequently, the Immune-Related Response Evaluation Criteria in Solid Tumors is currently more commonly employed to evaluate immunotherapy responses.

2. Literature search and selection

Our review focuses on the latest advancements regarding the use of artificial intelligence (AI) to predict immunotherapy outcomes in patients with NSCLC. We provide a summary of the search strategy in Table 1.

The search was performed in January 21, 2025 on the PubMed and Web of Science databases. The keywords used were subdivided into three categories: (i) tumor type, (ii) treatment, and (iii) methodology used for the analysis. Tumor type keywords included “non-small cell lung cancer” OR “NSCLC.” Treatment keywords included “immunotherapy” OR “immune checkpoint inhibition” OR “anti-PD-L1 therapy” OR “anti-PD-1 therapy” OR “PD-1 inhibitor” OR “PD-1 blockage” OR “neoadjuvant immunotherapy” OR “neoadjuvant chemoimmunotherapy.” Methodology keywords included “radiomics” OR “machine learning” OR “deep learning” OR “artificial intelligence” OR “pathomics” OR “multi-omics.” Furthermore, the exclusion criteria included secondary scientific literature (narrative review articles, systematic reviews, book chapters); special scientific literature (letters to the editor, correspondences, editorials, opinions, commentaries); pre-clinical studies; literature that is not in English; benign tumors; other types of tumors; studies without an immunotherapy cohort; studies lacking prediction of immunotherapy efficacy; and studies using machine learning or deep learning only in feature selection.

The literature screening process strictly followed the PRISMA 2020 guidelines. Initial searches across databases and clinical trial registers (chictr.org.cn; clinicaltrials.gov) identified 1,037 records (933 from databases and 104 from registers). After removing 327 duplicate records, 710 studies underwent title/abstract screening. Of these, 667 records were excluded for predefined reasons: 362 failed to meet methodological scope (Reason 1), 39 lacked peer-reviewed original research (Reason 2), and 266 were non-immunotherapy studies or involved non-lung cancer cohorts (Reason 3). Full-text retrieval was attempted for the remaining 43 reports, with 12 inaccessible due to paywall or data restrictions. Consequently, 31 studies fully complied with all inclusion criteria. These 31 included studies mainly employed radiomics, pathomics, or integrated multi-omics approaches, all focusing on AI-driven prediction of NSCLC immune therapy response. The details of the inclusion and exclusion of the literature are provided in Supplementary Material.

3. Biomarkers for predicting the immunotherapeutic efficacy of advanced NSCLC

Immunotherapy has transformed NSCLC treatment, but its clinical implementation faces challenges, such as varied response rates,[4,5] acquired resistance, and economic constraints. Established biomarkers including PD-L1 expression and tumor mutational burden (TMB) guide clinical decisions (Figure 1), while emerging candidates such as microsatellite instability, tumor microenvironment (TME) features, and circulating tumor DNA (ctDNA) profiles show promise (Table 2).

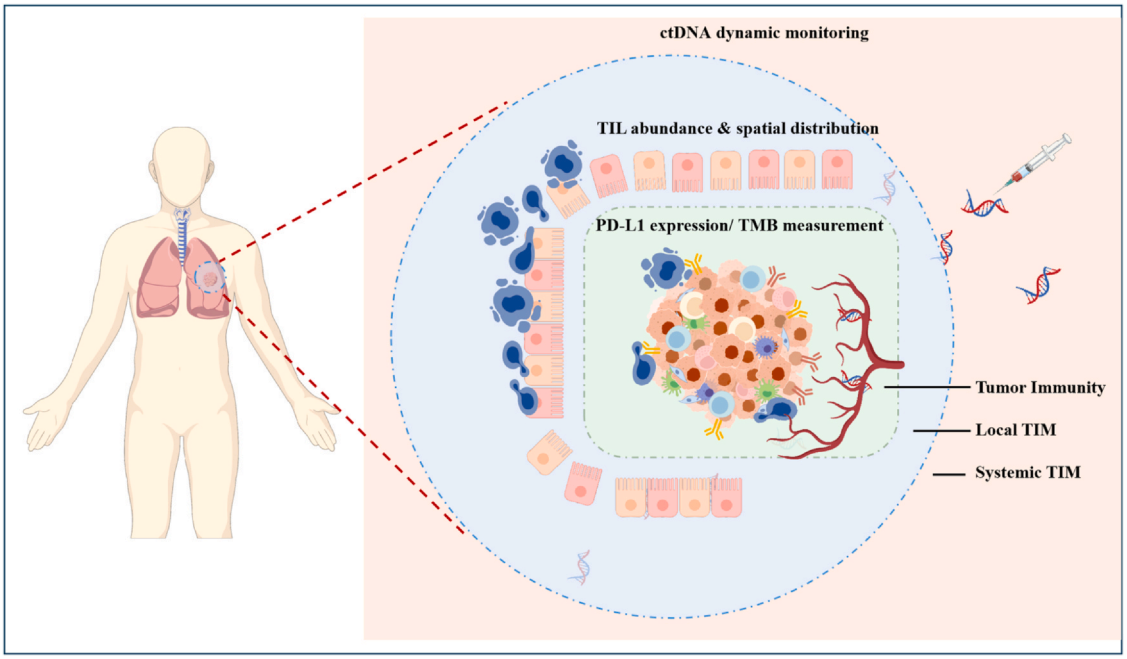


Figure 1. Tissue and blood-based biomarkers for immunotherapy response prediction. Abbreviations: 1. ctDNA: circulating tumor DNA 2. TIL: tumor-infiltrating lymphocyte 3. PD-L1: programmed death-ligand 1 4. TMB: tumor mutational burden 5. TIM: tumor immune microenvironment.

Table 2
Biomarkers of response to ICIs in NSCLC.

Biomarker	Tissue type	Sensitivity	Specificity	ORRs derived by biomarker cut-off	Cut-off	Tumor type	Agent	Data source
PD-L1	Tumor and blood	0.61	0.62	17% vs. 34%	PD-L1 ≥ 25%	NSCLC	Durvalumab + Tremelimumab	MYSTIC[6]
		0.7	0.64	12% vs. 36%	PD-L1 ≥ 25%	NSCLC	Durvalumab	
		0.58	0.58	25% vs. 38%	PD-L1 ≥ 50%	NSCLC	Atezolizumab	IMpower110[7]
		0.62	0.48	32% vs. 42%	PD-L1 ≥ 1%	NSCLC	Nivolumab	Checkmate9LA[8]
		0.68	0.53	9% vs. 19%	PD-L1 ≥ 1%	Non-squamous NSCLC	Nivolumab	CheckMate063[9]
		0.68	0.66	10% vs. 30.2%	PD-L1 ≥ 50%	NSCLC	Pembrolizumab	KEYNOTE－010[10]
TMB	Tumor and blood	/	/	9% vs. 57%	High TMB and TPS ≥50% vs Low TMB and TPS <1%	NSCLC	ICIs	Ricciuti et al. [11]
		/	/	18% vs. 43%	TMB ≥19 mut/Mb		ICIs	
		0.68	0.65	12% vs. 43.8%	TMB ≥10 mut/Mb	NSCLC	Nivolumab + ipilimumab	CheckMate 568 [12]
		/	/	5% vs. 47%	TMB ≥10 mut/Mb	NSCLC PD-L1 <1%		
		/	/	18% vs. 48%	TMB ≥10 mut/Mb	NSCLC PD-L1 ≥1%		
MSI-H/dMMR	Tumor and blood	/	/	40%	MSI-H/dMMR	15 types	Pembrolizumab	Keynote 016 164 012 028 158 [13]
TILs-CD8	Tumor	0.6	0.83	17% vs. 60%	CD8 count in 886/mm2–1899/mm2	NSCLC	Pembrolizumab or nivolumab	real world[14]
		0.71	0.69	13% vs. 45%	CD8 + /CD4 + ratios higher than 2	NSCLC		
TILs-CD39CD8	Tumor	1	0.857	0% vs. 64%	31.05% CD39 + /CD8 + of total CD8 + T cells	NSCLC	ICIs	real world[15]
LIPI(dNLR and LDH)	Blood	/	/	35% vs. 21% vs. 11%	Good/moderate/poor	NSCLC	(Nivolumab/pembrolizumab/atezolizumab/durvalumab/durvalumab-ipilimumab)	Mezquita et al.[16]
ctDNA	Blood	/	HR = 1.35	60% vs. 57%	Baseline ctDNA positive	NSCLC	ICIs	Zaman et al.[17]
		/	HR = 2.71	23% vs. 64%	Early reduction vs. high reduction during treatment	NSCLC		

Abbreviations: 1. ORRs: overall response rates 2. PD-L1: programmed death ligand-1 3. TMB: tumor mutational burden 4. MSI-H/dMMR: microsatellite instability-high/mismatch repair deficient 5. TILs: tumor-infiltrating lymphocytes 6. LIPI: immune prognotic index 7. dNLR: derived neutrophil-to-lymphocyte ratio 8. LDH: lactate dehydrogenase lung 9. ctDNA: circulating tumor DNA 10. NSCLC: non-small cell lung cancer 11. ICIs: immune checkpoint inhibitors.

PD-L1 remains the first Food and Drug Administration-approved predictive biomarker in United States, although its clinical utility is hampered by three key limitations: variability in immunohistochemical quantification methods[18–22]; interpretation complications from coexisting membrane-bound, soluble, and extracellular vesicle forms; and suboptimal sensitivity/specificity (<70%). AI demonstrates the potential to overcome these limitations through radiomic/pathologic analysis, thus enabling non-invasive PD-L1 status prediction with improved accuracy.[23] Tumor-infiltrating lymphocytes (TILs) in the microenvironment exhibit prognostic value,[18–21] but spatial heterogeneity and dynamic biomarker interactions hinder clinical translation.[22,24]

While landmark trials have established TMB as a predictive biomarker, its application is controversial: CheckMate studies revealed limited utility in non-squamous NSCLC, with epidermal growth factor receptor (EGFR)/anaplastic lymphoma kinase-driven tumors showing 58% reduced response despite high TMB.[25] Additional challenges include inconsistent TMB-high definitions and technical hurdles in standardizing dynamic pTMB monitoring.[26] Liquid biopsy biomarkers such as ctDNA/circulating free DNA demonstrate predictive potential across NSCLC stages,[27–29] although low-frequency mutation detection limitations and cost-effectiveness concerns restrict widespread adoption.[30,31]

Furthermore, the pan-cancer microsatellite instability-high/mismatch repair deficient biomarker shows limited NSCLC relevance due to low incidence (1.9% in 48,782 tumors)[32] and an unvalidated correlation with TMB. Systemic inflammatory markers including derived neutrophil-to-lymphocyte ratio and lactate dehydrogenase gain prognostic traction—elevated dNLR correlates with reduced immune checkpoint inhibitor efficacy[33]; the Lung Immune Prognostic Index that combines these parameters specifically stratifies survival outcomes in ICI-treated patients.[34]

Current biomarker strategies are faced with spatiotemporal heterogeneity and measurement standardization issues. Mechanistically relevant emerging markers (LAG-3, tumor-resident memory T cells, and NUSAP1)[35–37] and AI-driven multianalyte integration approaches represent promising directions for developing dynamic prediction systems in precision immunotherapy.[38]

4. Application of radiomics in predicting the therapeutic efficacy of NSCLC

Radiomics, a noninvasive imaging analytics tool, quantifies medical image features to uncover correlations with therapeutic responses and clinical outcomes.[39,40] This approach integrates tumor imaging data with clinical, genetic, and histologic profiles to derive predictive biomarkers for diagnosis, treatment response, and prognosis.[41] Thoracic computed tomography (CT) scans, routinely used in lung cancer management, provide rich datasets for radiomic analysis. AI-enhanced radiomics reduces overdiagnosis and false positives in lung cancer screening,[42] while radiomic signatures successfully differentiate lung adenocarcinoma from granulomatous nodules[43] and indolent tumors.[44] Figure 2 delineates the developmental progression of AI-driven predictive frameworks in lung cancer immunotherapy (2015–2024),

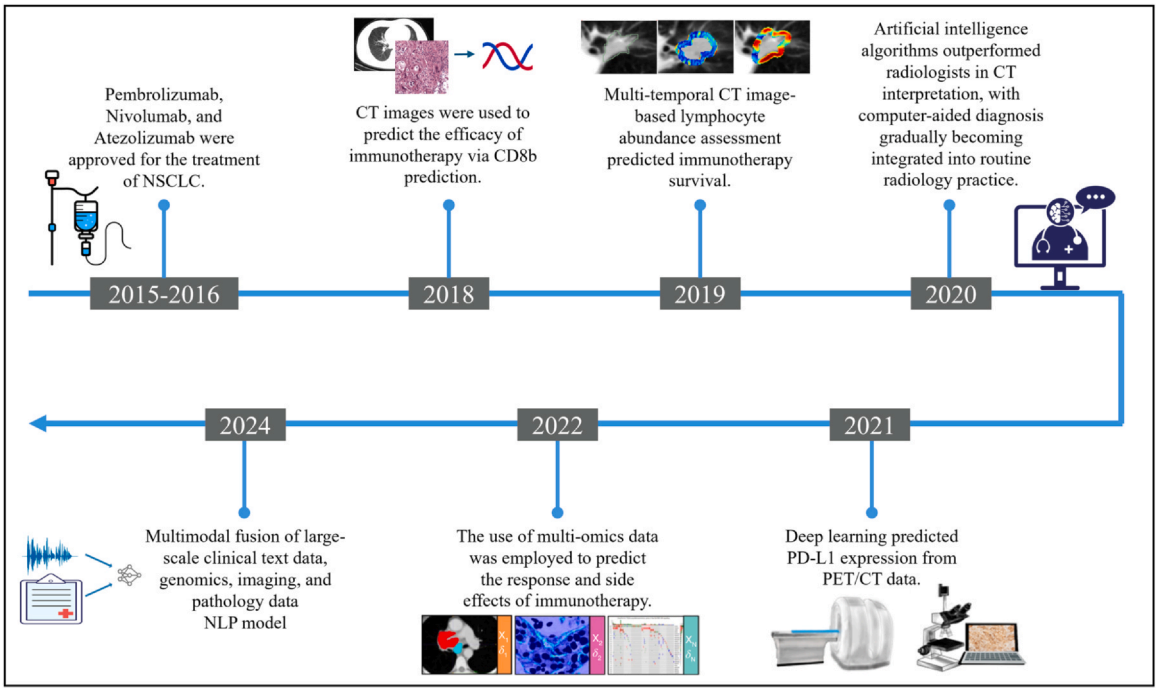


Figure 2. The evolutionary trajectory of AI-driven predictive models in lung cancer immunotherapy: from early biomarker discovery to multimodal dynamic monitoring systems. Abbreviations: 1. NSCLC: non-small cell lung cancer 2. CT: computed tomography 3. NLP: natural language processing 4. PD-L1: programmed death-ligand 1 5. PET-CT: positron emission tomography–computed tomography.

highlighting the technological convergence across radiogenomic profiling, liquid biopsy integration, and dynamic tumor microenvironment mapping.

4.1. Image acquisition and preprocessing

Baseline CT imaging is universally adopted across studies, although acquisition protocols vary significantly. Only two reviewed studies omitted specific CT parameters.[54] Multicenter heterogeneity (e.g., slice thickness, respiratory artifacts) necessitates preprocessing, exemplified by Mu et al.'s PET/CT voxel resampling ($1 \times 1 \times 1\,mm^3$)[61] and Liu's 512×512 pixel convolution kernel reconstruction[49] to standardize data.

4.2. Tumor segmentation challenges

Image segmentation, critical for defining regions of interest, faces challenges in advanced NSCLC due to irregular tumor boundaries and complex tumor-adjacent tissue interfaces. Manual delineation remains predominant,[55,62] although Sun et al. standardized tumor burden assessment via whole-lesion segmentation (threshold ≥ 5 mm),[58] and Trebeschi et al. improved response prediction accuracy through exhaustive manual segmentation.[46] While 3D tumor volumes are prioritized, peritumoral analysis (e.g., Vaidya et al's 15-mm and Khorrami et al's 30-mm expansions) enhances predictive performance but risks overfitting.[54,58,45,63,59]

4.3. Feature extraction and selection

Feature extraction leverages MATLAB or PyRadiomics platforms, followed by least absolute shrinkage and selection operator, logistic regression, or minimum redundancy maximum relevance -based feature selection. Mu et al. addressed tumor heterogeneity via subtype-stratified least absolute shrinkage and selection operator modeling (squamous vs. adenocarcinoma), thereby generating a multiparametric radiomic signature.[61] Furthermore, multimodal integration challenges are mitigated by Tunali et al.'s logistic regression framework[64] and Vaidya et al's dynamically weighted mRMR algorithm.[54]

4.4. Machine learning model development and clinical validation

The field of machine learning has witnessed significant advancements, particularly in the development and clinical validation of models for medical applications.[65,66] For immunotherapy response prediction, machine learning innovations include Trebeschi et al's[46] and Dercle et al's[67] biologically informed random forest models and Liu et al.'s SVM-LRC-GNB consensus system.[49] The Simple Temporal Attention (SimTA) module was designed for analyzing asynchronous time series in 2020.[68] Yang et al. resolved temporal data misalignment with SimTA, thus enabling dynamic biomarker integration.[52] Multi-omics breakthroughs, such as the radiomics-derived TMB with exosomal PD-L1 model (100% sensitivity/specificity), link imaging traits to molecular mechanisms.[53] Radiomics predicts immunotherapy outcomes across cancers, with NSCLC outperforming melanoma (area under the curve [AUC] 0.76 vs. 0.67).[46] Columbia University's CT-based model achieved an AUC of 0.92 for melanoma overall survival (OS) prediction.[69] In addition. radiomic-CD8 correlations (AUC 0.76 for immune-inflamed vs. desert tumors)[58] and TMB radiomic biomarkers (an AUC of 0.85 for TMB ≥ 10 mut/Mb)[55] demonstrate clinical utility. This high performance underscores the potential of CT-derived biomarkers in predicting immunotherapy outcomes. Accurate PD-L1 expression assessment remains a critical yet challenging biomarker for patient selection so significant efforts have focused on developing non-invasive deep learning surrogates for PD-L1 status.[70,71] Deep learning-derived PD-L1 surrogates (AUC > 0.8) rival IHC in survival prediction,[60] while Yoon et al.'s radiomic-clinicopathologic model predicts PD-L1 $\geq 50\%$ (AUC $= 0.84$).[56]

4.5. Peritumoral radiomics and immune microenvironment

Peritumoral radiomics, reflecting an immune microenvironment dynamics, shows promise[72]. Khorrami et al. linked peri-tumor Gabor features to TIL density and PD-L1 expression.[45] Despite progress, radiomics faces interpretability gaps between imaging features and immunotherapy mechanisms. Most studies overlook peritumoral data, thus limiting insights into NSCLC's immune microenvironment. A comprehensive overview of direct/indirect prediction approaches is summarized in Table 3.

Table 3
A summary of the radiomics for directly and indirectly predicted immunotherapy.

Research types	Centers	Tumor entity	Groups		Study endpoints		Data modules	Timepoints acquired for CT scans	Segmentation methods	Lesion choice	Region of interest	Feature extraction algorithms	AUC of training cohort	AUC of validation cohort
			Training cohort	Validation cohort	Primary endpoint	Secondary endpoint								
Retrospective & prospective study [45]	2	Advanced NSCLC (M1)	50	42/27	Response based on RECISTv1.1	OS	CE-CT	Multiple	3D-slicer semi-auto delineation	Target lesions	Target lesions + 30 mm perinodular radius	WLCX	0.88	0.85/0.81
Retrospective study [46]	2	Metastatic melanoma/ NSCLC	133	70/262/39	Response based on RECISTv1.1	OS	CE-CT	Multiple	Manual	Measurable target lesions	Target lesions	LR/RF/GE	0.83/0.78/ 0.64	0.76
Retrospective & prospective study [47]	1	Advanced NSCLC (IIIB-IV)	99	47/48	DCB (PFS = 6 months)	OS, PFS	PET/CT	Single	Semi-auto delineation	Measurable target lesions	Target lesions	LASSO	0.86	0.83/0.81
Retrospective study [48]	1	Advanced NSCLC	228	/	TTP = 2 months; HPD	/	CT	Single	/	Largest measurable lesions	Tumor lesions and tumor border regions	LR	0.804/0.865	/
Retrospective study [49]	1	NSCLC IIIB/IV	46	/	PFS, OS	Response	CE-CT	Single	Manual	Largest measurable lesions	Target lesions	/	PFS: 0.73 ± 0.07 OS:0.60 ± 0.08	/
Retrospective study [50]	3	Advanced NSCLC (IIIB-IV)	35	24	OS	PFS	CE-CT	Multiple	/	Target lesions	Target lesions	/	/	/
Retrospective study [51]	9	NSCLC	137	60 + 161 (time-dependent analysis)	ORR for 6 months	PD-L1	Plain CT	Multiple	ITK-SNAP manual delineation	Largest target lesion vs. target lesions	Target lesions	MRMR/ LASSO	Delta-Rad: 0.81 Nomogram: 0.83	Delta-Rad: 0.80 Nomogram: 0.83
Retrospective study [52]	1	NSCLC IIIB-IV	200	/	Response for 60 and 90 days based on RECISTv1.1	/	CT/blood test	Multiple	Manual delineation	Target lesions with a diameter ≥5 mm	Target lesions	/	0.77 (60 days), 0.80 (90 days)	/
Retrospective study [53]	1	Local advanced/ advanced NSCLC	38	/	PFS, ORR, CBR	/	Non-contrast CT/blood sample	Single	Manual delineation	Entire primary tumor lesion	The largest cross-sectional area	/	/	/
Retrospective study [54]	1	NSCLC I-IV	109	/	Response based on RECISTv1.1	/	CT	Single	3D-slicer manual delineation	Largest target lesions	Target lesions + 0 mm–15 mm perinodular radius	MRMR	0.85	0.96
Retrospective study [55]	1	LUAD/LUSC + advanced NSCLC III + IV	236	26/65/123	TMB score	OS, PFS	CT	Single	3D-slicer semi-auto delineation	Entire primary tumor lesion	Target lesions	Deep learning	TMBRB: 0.85 Rad: 0.75	TMBRB: 0.81 Rad: 0.74
Retrospective study [56]	1	LUAD(> IIIA)	153	/	PD-L1 positivity	/	CE-CT	Single	Semi-automatic	Entire primary tumor lesion	Target lesions	LASSO	0.661	
Retrospective study [57]	1	NSCLC	260	130	PD-L1 expression	/	CT	Single	Manual ITK-snap kit	Entire primary tumor lesion	The largest cross-sectional area	LASSO	Rad : 0.786 Rad + clinicopatho-logic features: 0.829	Rad: 0.807 Rad + clinicopathologic features: 0.848
Retrospective study [58]	1	Incurable or metastatic solid tumors	135	119/100/137	Concordance of the radiomic signature (CD8B)	/	CE-CT + RNAseq	/	Semi-auto delineation ISO gray	Biopsied lesion, primary lesion, biggest lesion	Tumor boundaries by 2 mm on each side	ENRRM	0.74	0.67/0.76
Retrospective study [59]	7		94	/	Response based on RECISTv1.1		CE-CT	Multiple		Any tumor with diameter	Tumor boundaries	ENRRM	Response AUC 0.63,	Out of field AUC 0.70,

(*continued on next page*)

Table 3 (*continued*)

Research types	Centers	Tumor entity	Groups		Study endpoints		Data modules	Timepoints acquired for CT scans	Segmentation methods	Lesion choice	Region of interest	Feature extraction algorithms	AUC of training cohort	AUC of validation cohort
			Training cohort	Validation cohort	Primary endpoint	Secondary endpoint								
		Advanced or metastatic solid tumors				Clinical outcome, PFS, OS			Semi-auto delineation ISO gray	≥ 5 mm at baseline	by 2 mm on each side		PFS: P = 0.040, HR = 1.67 OS : P = 0.023,	OS: HR = 2.08, P = 0.023
Retrospective study[53]	1	NSCLC IV	38	/	PD, PR, SD	PD-L1 expression	Plain CT	Single	Manually	Primary tumor lesion	/	LASSO	Specificity : 100% Sensitivity: 85.71% AUC: 0.96	/
Retrospective & prospective study[60]	3	NSCLC	284	116/114/217	PD-L1 positivity,/ PFS, OS		^{18}F-FDG PET/CT	One month before biopsy	Manually ITK-snap kit	Primary tumor lesion	Entire tumor and peripheral region	SResCNN	0.89	0.84/0.82/0.82

Abbreviations: 1. NSCLC: non-small cell lung cancer 2. LUAD: lung adenocarcinoma 3. LUSC: lung squamous cell carcinoma 4. RECIST: Response Evaluation Criteria in Solid Tumors 5. DCB: drug-coated balloon 6. PFS: progression-free survival 7. TTP: time to progression 8. HPD: hyperprogressive disease 9. OS: overall survival 10: ORR: overall response rate 11. CBR: clinical benefit rate 12. PD-L1: programmed death-ligand 1 13. PD: disease progression 14. PR: partial response 15. SD: disease stabilization 16. CE-CT: contrast-enhanced computed tomography 17. PET/CT: positron emission tomography/computed tomography 18. WLCX: Wilcoxon rank sum 19. LR: logistic regression 20. RF: random forest 21. GE: genetic evolution 22. LASSO: least absolute shrinkage and selection operator 23. MRMR: minimum redundancy maximum relevance 24. ENRRM: elastic-net regularized regression method 25. SResCNN: small residual-convolutional neural network 26. TMBRB: tumor mutational burden radiomic biomarker 27. AUC: area under the curve 28. HR: hazard ratio.

5. Deep learning in computational pathology for immunotherapy prognostication

Computational pathology has emerged as a transformative tool in immunotherapy biomarker discovery; it enables the quantitative analysis of histopathological features beyond human visual perception.[73,74] While traditional pathology provides diagnostic gold standards, AI-enhanced methods now decode TME heterogeneity through hematoxylin and eosin (H&E) staining slides and IHC analysis.[75–77] Early applications focused on semiquantitative morphometric profiling in cancer prognosis,[78] while recent advances target immune-oncology through three key approaches, which are described below.

5.1. PD-L1 quantification refinement

Automated tumor proportion score analysis addresses inter-pathologist variability in PD-L1 assessment across IHC assays (22C3/SP263). Kapil et al.[79] demonstrated that 270 NSCLC biopsies analyzed via SP263-based deep learning revealed concordance with manual scoring, but struggled with weak-positive regions. Dual-scale categorization improved reliability by subclassifying positive regions.[80] U-ResNet achieved cross-assay generalizability (22C3/SP263) and even predicted PD-L1 status directly from H&E slides (AUC = 0.8),[81] although this was limited by small training cohorts and immune cell interference.[82]

5.2. TMB prediction from histology

To overcome whole-exome sequencing limitations, Chen et al.[83] achieved modest TMB stratification via H&E image analysis, while Sadhwani's convolutional neural network-clinical fusion model, developed by Sadhwani et al.[84], matched a weakly supervised approach. State-of-the-art weakly supervised frameworks predict pan-cancer TMB (AUC = 0.82) and spatial heterogeneity, although external validation performance drops due to overfitting. Model interpretability remains critical for clinical adoption.

5.3. TIL mapping and therapeutic prediction

Park et al's deep learning algorithm objectively classified TME into three immune phenotypes (inflamed; desert; and excluded phenotypes), achieving a ROC of > 0.9. The inflamed subtype with PD-L1 $\geq 50\%$ showed superior immunotherapy response, thus establishing TILs as complementary biomarkers.[85] Pioneering research by Hu[81] (AUC = 0.64–0.78 by multicancer validation) demonstrated cross-sample applicability, despite limitations in using IFN-γ surrogates without clinical response data.

The key obstacles here include 1) whole-slide image preprocessing variability (256 × 256 vs. 512 × 512 patches affecting structural fidelity)[86]; 2) temporal disconnect between diagnostic biopsies and late-line immunotherapy; 3) invasive sampling constraints versus radiomics' longitudinal advantages. Emerging multimodal models combining CT, next-generation sequencing, and histopathology outperform single modality models,[87] although these models require multicenter validation and standardized feature extraction.

6. AI-driven integration of multiscale biomarkers

Recent advances in multimodal AI have revolutionized the integration of radiomic, tissue and blood-based biomarkers, thus creating synergistic frameworks for predicting immunotherapy responses in both advanced and early-stage NSCLC (Figure 3). By dynamically synthesizing complementary data streams across spatial and temporal dimensions, these AI systems provide unprecedented insights into tumor-immune ecosystem dynamics.

Three pioneering approaches in advanced NSCLC demonstrate AI's capacity to connect imaging phenotypes with molecular mechanisms.

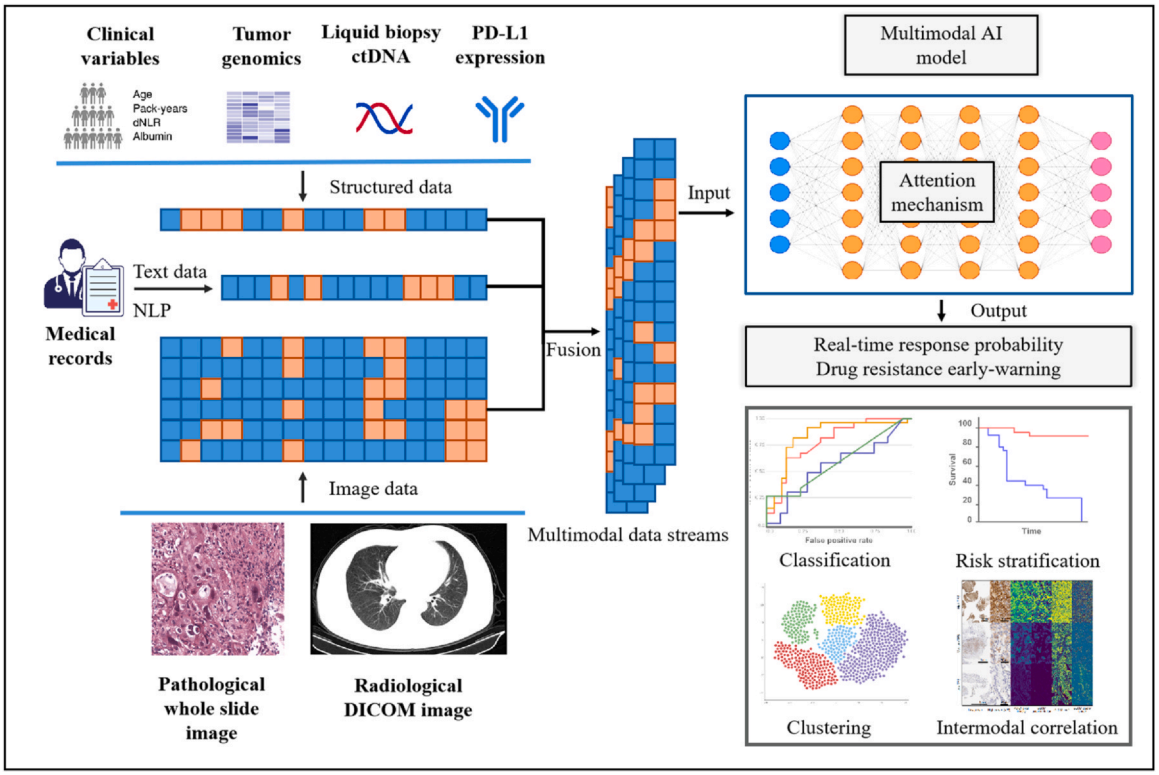


Figure 3. Workflow of AI-based multimodal immunotherapy response prediction. This diagram illustrates a machine learning pipeline for immunotherapy outcome modeling. The key stages include: multimodal data collection, data preprocessing and feature engineering, predictive model development, and comprehensive performance validation. The representative PD-L1 IHC slides were reprinted from Vanguri et al.; the multimodal integration of radiology, pathology, and genomics for prediction of response to PD-L1 blockade in patients with non-small cell lung cancer are licensed under CC BY 4.0 from Springer Nature.[87] Other graphical elements were all designed via biogdp.com.

Abbreviations: 1. ctDNA: circulationg tumor DNA 2. PD-L1: programmed death ligand-1 3. NLP: natural language processing 4. DICOM: digital imaging and communications in medicine.

Tong et al.[88] established a PET/CT radiomics–clinical fusion model that deciphers immune landscapes through metabolic spatial patterns (standardized uptake value entropy) and clinical parameters (gender/pathology subtypes) and achieved 82% accuracy in CD8+ T-cell stratification. While this imaging-centric approach effectively captures tumor heterogeneity, its limited genomic integration leaves evolutionary trajectories unmapped. Addressing this gap, Ai et al.[89] engineered a liquid biopsy-powered predictor to track real-time tumor dynamics through ctDNA clearance rates and blood-based TMB evolution. Their model achieved an AUC of 0.89 in predicting durable clinical benefit by quantifying two critical dimensions: structural genomic instability (blood-based TMB) and temporal response patterns (ΔctDNA). Concurrently, Vanguri et al.[87] developed DyAM—a dynamic attention network that automatically weights CT texture features, PD-L1 histology scores, and mutational signatures. This adaptive integration outperformed single-modal biomarkers (ΔAUC +0.07 vs. PD-L1 alone), thereby revealing how AI can resolve the spatial discordance between radiographic features and molecular profiles.

In the neoadjuvant setting, recent studies have demonstrated significant progress in developing AI models that leverage diverse data sources to enhance chemoimmunotherapy prediction accuracy. Han et al.[90] developed a weakly supervised deep learning model based on whole-slide images to predict major pathological responses by identifying histological features associated with treatment response. Liu et al.[91] achieved an AUC of 0.88 in predicting pathological complete response using ^{18}F-FDG PET/CT radiomics. Additionally, Huang et al.[92] highlighted spatial context by integrating intratumoral and peritumoral radiomics features within a 15-mm radius from the tumor margin, thus significantly improving major pathological response prediction. Temporal dynamics were addressed through delta-radiomics: Han et al.[93] leveraged baseline and pre-operative CT scans to achieve an AUC of 0.85 for major pathological response prediction, while Yang et al.[94] validated multitime-point models that outperformed single-phase analyses. She et al.[78] further bridged imaging and biology via a deep learning model that integrates multiphase CT data (AUC = 0.87), thereby revealing associations between low predictive scores and tumor proliferation pathway activation.

The integration of multiscale biomarkers through AI faces three interconnected challenges that require sophisticated computational solutions. First, temporal synchronization poses a significant hurdle due to mismatched data acquisition timelines across modalities. Jee et al.[95] addressed this through temporal transformers that align longitudinal radiomics with sporadic genomic sampling and continuous clinical narratives, although variations in institutional data capture protocols persist. Neoadjuvant studies highlight the value of dynamic imaging: Han's delta-radiomics and Yang's model demonstrate how temporal feature evolution improves response prediction. Second, the reconciliation of multi-omics discordance demands advanced analytical frameworks, as exemplified by Han et al.'s[96] consensus machine learning-related prognostic signature system that employs graph neural networks to resolve conflicts between mRNA expression surges, lncRNA regulatory effects, and methylation silencing patterns, thus successfully identifying aggressive lung adenocarcinoma subtypes with hypoxic microenvironments (HR = 3.21, $P < 0.001$). Third, modality compensation emerges as critical for clinical practicality. Captier et al.[97] pioneered cross-modal imputation using generative adversarial networks that reconstruct transcriptomic profiles from routine CT scans when molecular testing is unavailable, thus achieving clinically meaningful concordance (C-index = 0.78). In neoadjuvant contexts, Huang et al's[92] peritumoral radiomics and She et al's[78] multiphase CT integration exemplify how spatial and temporal compensation enhances practicality.

Current limitations highlight critical translational barriers. While Tong's radiomics model shows clinical practicality (requires only baseline imaging),[88] its static nature fails to capture ctDNA-quantified clonal dynamics demonstrated by Ai et al.[89] Conversely, liquid biopsy approaches face temporal sampling constraints. The protocol described by Ai et al requires 5 serial draws over 12 weeks. Vanguri's DyAM model provides a middle ground through missing modality compensation, maintaining an AUC of 0.75 even with 30% data absence.[87] For neoadjuvant applications, while multiphase imaging improves accuracy (Han's delta-radiomics), it increases clinical workflow complexity.[93] She et al.'s biological correlation analysis remains exploratory, requiring validation in prospective trials.[78]

To realize clinical implementation, three priorities emerge: temporal fusion architectures for asynchronous multi-omics integration, particularly critical for aligning neoadjuvant therapy response biomarkers, such as delta-radiomics, with post-treatment pathology; standardization of radiogenomic mapping protocols across imaging platforms, extending to peritumoral zone definitions (e.g., Huang's 15-mm radius[92]) and delta-feature calculation methods; and federated learning frameworks that address data privacy while capturing population heterogeneity, which is essential for validating neoadjuvant models across institutions.

As these multimodal systems evolve, they promise to dissolve traditional boundaries among radiological phenotypes, histological patterns, and liquid biopsy dynamics, ultimately creating unified biomarkers for precision immuno-oncology across the disease continuum from neoadjuvant stratification to metastatic response monitoring.

7. Future directions: interpretable AI and ethical considerations

The application of radiomics and pathomics in therapeutic efficacy prediction faces marked challenges, particularly regarding the inherent interpretability limitations of complex deep learning systems. While these "black box" models demonstrate superior predictive performance, the opacity of their decision-making processes raises critical concerns for clinical deployment. Ensuring model interpretability serves dual purposes: enhancing operational safety through verifiable reasoning pathways and maintaining compliance with evolving ethical AI regulations. Beyond technical necessity, interpretability becomes an ethical imperative in healthcare contexts. Clinicians bear the ultimate responsibility for treatment decisions, and opaque predictions risk undermining informed consent processes. Patients have the right to understand how AI-derived recommendations align with their unique biological characteristics. Thus. strategic architectural innovations are now enabling researchers to reconcile predictive power with biological plausibility.

Data governance presents another ethical frontier. A landmark advancement comes from Wang et al.,[80] who developed the Ceograph framework that incorporates stratified pooling architectures (subgroup and global mean pooling layers). This design enables the simultaneous identification of cell-level decision drivers and population-level feature importance through model-agnostic analysis. In predicting EGFR tyrosine kinase inhibitor therapy response, their approach revealed quantifiable morphological determinants—increased tumor cell eccentricity correlated with nonresponse probability ($P < 0.01$), while squamous cell carcinoma exhibited 23% higher cellular solidity than adenocarcinoma subtypes. Such layered interpretability bridges computational pathology with traditional histopathological biomarkers through statistically grounded biological explanations.

Traditional architectures also demonstrate clinical-grade interpretability when appropriately implemented. Convolutional neural networks generate anatomically aligned heatmaps via GradCAM visualizations,[98] whereas Transformer models expose feature prioritization through self-attention distributions.[82] While these techniques enable the validation of biologically relevant focus areas, they also expose ethical questions regarding data provenance. Training datasets must adhere to findable, accessible, interoperable, reusable (FAIR) principles, with explicit documentation of demographic distributions to audit for representation biases. For example, the underrepresentation of ethnic minorities in EGFR mutation studies could perpetuate healthcare disparities if unaddressed.

Furthermore, three complementary strategies enhance model transparency: feature correlation analysis systematically evaluates radiomic features (e.g., GLCM texture, GLRLM patterns) against immunological profiles and clinical outcomes, thus revealing mechanistic drivers such as the high-weight interpretable feature nuclear-cytoplasmic ratio, which shows strong correlation with PD-L1 expression levels ($r = 0.68$); multiplex spatial biology leverages advanced staining platforms (mIHC/mIF/IMC) to map cellular ecosystems, exemplified by Shu et al.'s work that demonstrates that CD20+ and CXCL13+ lymphoid aggregates quantified via imaging mass cytometry predicted immunotherapy response with 89% specificity, outperforming conventional H&E assessment by 22%;[99] and synthetic imaging synthesis employs cross-modal generation techniques, which includes conditional generative adversarial networks by Salehjahromi et al., achieving 0.92 structural similarity in PET synthesis from CT scans[100] and Zhou et al.'s Multimodal-Attention-based virtual mIF Staining (MAS) preserving 94% diagnostic concordance with physical mIF slides in gastric cancer prognosis to extract latent biological information from existing imaging data.[101]

The clinical adoption of multimodal diagnostics requires integrated analytical frameworks, as exemplified by Niu et al.'s M3FM model,[102] which simultaneously processes 3D CT scans, demographic data, and clinical history to achieve multitask prediction (AUC = 0.91 for lung nodule malignancy detection). However, substantial challenges remain. Overfitting risks persist due to limited cohort sizes (median training $n = 423$ across the reviewed studies), thereby restricting model generalizability. Cross-institutional validation is further complicated by confounding variability, spanning both technical factors including CT reconstruction algorithms and biological diversity such as ethnic differences in EGFR mutation prevalence. Additionally, while synthetic imaging reduces staining costs, integrating multimodal AI systems (e.g., MAS) into clinical workflows demands specialized computational pathology infrastructure, thus creating practical implementation barriers.

Prospective multicenter trials require dual-dimensional standardization. Technically, protocols must unify radiomic analysis criteria, including peritumoral zone definitions and delta-radiomics computation, while advancing dynamic interpretability frameworks to adapt to evolving tumor ecosystems. Concurrently, confounder-aware architectures should explicitly model technical variability (e.g., imaging parameter discrepancies) and biological heterogeneity (e.g., molecular subtypes). Ethically, an ethics-by-design framework must integrate dynamic consent mechanisms for the reuse of longitudinal data, algorithmic impact assessments to monitor prediction biases across subgroups, and independent review boards with specialized AI governance expertise. This dual focus ensures both methodological rigor and equitable implementation.

Furthermore, clinical translation demands a three-tier validation paradigm. First, technical validation confirms model robustness across multicenter datasets. Second, mechanistic validation employs causal inference to map AI-identified radiomic features to therapeutic mechanisms, thus replacing opaque predictions with biologically grounded insights. Finally, clinical validation requires randomized trials to verify the utility of AI-derived biomarkers in therapeutic decision-making. This evolution—from "black box prediction" to "mechanistic collaboration"—redefines AI as a co-explorer in tumor biology, thus propelling precision oncology into an interpretable and actionable era.

8. Conclusions

AI emerges as a transformative tool that integrates radiomics, pathology, and multi-omics to decode tumor-immune dynamics and predict therapeutic outcomes. By analyzing imaging, histopathology, and

molecular data, AI enables noninvasive stratification of patients and real-time monitoring of resistance. The key challenges here include technical standardization, biological complexity, and model interpretability. Future progress hinges on ethical frameworks, cross-institutional validation, and clinical translation of AI-derived biomarkers. This synergy of technology and biology promises to advance precision immuno-oncology, thereby optimizing personalized therapeutic strategies for improved patient outcomes.

CRediT authorship contribution statement

Yangzhong Guo: Data curation. **Haiyu Zhou:** Writing – review & editing, Project administration, Methodology, Funding acquisition, Conceptualization. **Shaowei Wu:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Anzi Zhuang:** Writing – original draft, Resources, Investigation. **Gengda Huang:** Writing – original draft, Methodology, Data curation. **Ziyi Zhao:** Writing – original draft. **Weijie Zhan:** Methodology, Data curation. **Yu Lei:** Writing – review & editing, Methodology. **Yubo Zhou:** Data curation. **Chusong Li:** Formal analysis. **Lintong Yao:** Software, Resources.

Consent for publication

Not required.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are Authors' contributions appropriately investigated and resolved.

Reporting checklist

The authors have completed the Narrative Review reporting checklist.

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.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.intonc.2025.05.001.

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