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Decoding genomic heterogeneity in ground-glass nodule lung adenocarcinoma before radiotherpay: Subtype-driven biomarkers and therapeutic vulnerabilities

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► ***Original article***

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ABSTRACT

Background: Ground-glass nodules (GGNs) represent early-stage lung adenocarcinoma (LUAD) and exhibit substantial genomic and radiomic heterogeneity. Integrating computed tomography (CT) radiomic features with genomic and epigenomic alterations may improve prediction of nodule progression and radiotherapy response. ***Materials and Methods:*** A systematic literature search was conducted across PubMed, Scopus, and Web of Science (2010–2024) using predefined terms related to GGNs, radiogenomics, LUAD, CT radiomics, and radiosensitivity. Studies were included if they reported (1) human GGN data, (2) genomic or epigenomic characterization, and (3) radiomic features or CT phenotypes. Two reviewers independently screened articles, extracted data, and validated radiogenomic associations. ***Results:*** A total of 4,820 patients from eligible studies were analyzed. Distinct CT radiomic features - including attenuation, solidity ratio, textural entropy, vascular convergence, and shape irregularity - corresponded with recurrent genomic drivers. EGFR-mutant GGNs typically presented as pure or mixed GGNs with smooth margins, whereas KRAS-, TP53-, and KEAP1/NRF2-altered lesions showed higher solidity and increased heterogeneity. Radiomic complexity correlated with mutational burden, copy-number alterations, and pathway dysregulation in PI3K/AKT/mTOR, MAPK, Hippo/YAP, and TGF-β signaling. Several radiogenomic signatures also corresponded to predicted radiosensitivity or radioresistance, particularly features associated with oxidative stress pathways and immune microenvironment states. ***Conclusion:*** Radiogenomic integration provides critical insight into the biological heterogeneity of GGN-associated LUAD. CT radiomic features reflect underlying genomic alterations and may predict progression and radiotherapy responsiveness. This review establishes a structured framework for the radiogenomic interpretation of GGNs and outlines future applications in precision oncology and radiotherapy planning.

INTRODUCTION

The advent of high-resolution computed tomography (HRCT) has revolutionized the early detection of pulmonary ground-glass nodules (GGNs), with lung adenocarcinoma (LUAD) manifesting as GGNs now accounting for more than half of screen-detected malignancies [1, 2]. However, this radiological triumph has unveiled a persistent clinical paradox: while some GGN-associated LUADs remain indolent for years, others rapidly evolve into invasive or metastatic disease [3, 4]. Traditional radiological classification - categorizing lesions as pure, mixed, or solid-dominant based on the proportion of ground-glass opacity - fails to reliably predict biological behavior or therapeutic responsiveness. For instance, up to 30% of mixed GGNs with <50% solid components exhibit unexpected pathological invasiveness, whereas certain solid-dominant nodules demonstrate prolonged radiological stability [5]. This discordance between imaging phenotype and biological aggressiveness underscores the urgent need to redefine GGN-LUAD taxonomy through a genomic and molecular lens.

Longitudinal cohort studies reveal that approximately 22% of radiologically stable pure GGNs harbor occult *KRAS* G12C mutations yet maintain five-year progression-free survival rates exceeding 90%, in stark contrast to *EGFR*-mutant mixed GGNs exhibiting only 48% survival despite similar imaging features [6-8]. Spatially resolved multi-region sequencing has further exposed the profound intratumoral heterogeneity of these lesions: pure GGNs often display monoclonal evolution with APOBEC mutational signatures, whereas mixed and solid subtypes show branched evolutionary trajectories driven by chromosomal instability and *TP53* co-mutations [9].

Therapeutic inertia in GGN-LUAD management arises not from the absence of druggable targets, but from the failure to align emerging genomic and epigenomic biomarkers-such as *STK11*-deficient

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immune deserts, *HER2*-amplified microdomains, or *MET* exon 14 skipping mutations-with subtype-adapted treatment strategies [10-12]. Increasing evidence demonstrates that genomic heterogeneity, rather than radiographic morphology, dictates clinical outcomes and therapeutic sensitivity [13]. This realization has catalyzed efforts to integrate genomic, transcriptomic, and radiomic datasets into unified models capable of predicting biological aggressiveness and treatment response.

CT-based radiologic features of GGNs including attenuation, solidity, margin sharpness, lobulation, bubble-like lucencies, vascular convergence, textural uniformity, and model-derived radiomic signatures-frequently parallel the underlying molecular behavior of LUAD. EGFR-mutant GGNs typically manifest as pure or mixed GGNs with smooth, well-defined margins and low textural entropy, whereas lesions harboring KRAS, TP53, KEAP1/NRF2, or RBM10 alterations often display increasing solidity, irregular borders, or heterogeneous radiomic textures. These radiomic–genomic correspondences suggest that CT imaging can noninvasively reflect biological aggressiveness, mutational burden, pathway activation, and stromal or immune microenvironment states.

Key unresolved questions remain: How do spatially distinct driver events such as preferential *KRAS* G12C mutations in indolent pure GGNs versus *EGFR* L861Q variants in aggressive mixed subtypes govern phenotypic plasticity? What epigenetic mechanisms, including *CDKN2A* hypermethylation and H3K27me3-mediated chromatin remodeling, facilitate the transition from preinvasive to invasive adenocarcinoma? And crucially, can multi-omic integration uncover subtype-specific therapeutic and radiotherapeutic vulnerabilities obscured by conventional histopathology?

This review aims to address these questions by systematically decoding the genomic and radiogenomic architecture of GGN-LUAD subtypes. We synthesize emerging evidence from single-cell sequencing, spatial transcriptomics, and longitudinal liquid-biopsy studies to delineate three biological pillars of subtype evolution:

(1) driver event hierarchies that initiate and sustain subtype divergence,
(2) evolutionary bottlenecks shaping clonal dynamics during malignant transformation, and
(3) immune–microenvironment crosstalk that governs therapeutic resistance and radiosensitivity.

By anchoring these mechanisms to clinical translation - such as exploiting *MET* exon 14 skipping mutations in mixed GGNs or leveraging *TP53/ATM*-deficient subtypes for radiosensitization - we propose a paradigm shift from passive radiologic surveillance to precision interception. Ultimately, integrating multi-omic profiling with radiotherapy-adaptive strategies may transform GGN management from empiric observation to biologically guided intervention .

MATERIALS AND METHODS

Search strategy

A systematic literature search was performed using PubMed, Scopus, and Web of Science from January 2010 to January 2024. Search terms included “ground-glass nodules” , “lung adenocarcinoma,” “radiogenomics”, “CT radiomics”, “genomic heterogeneity”, “epigenetic regulation” and “radiosensitivity”.

Inclusion criteria

1. Human studies involving GGNs or early-stage LUAD.
2. CT-based imaging features or radiomic analyses.
3. Genomic, epigenomic, or transcriptomic profiling.
4. Studies evaluating progression, invasiveness, or radiotherapy response.

Exclusion criteria

Animal-only studies, case reports, editorials, commentaries, or articles without extractable radiomic data and studies lacking genomic or imaging correlation, were exlucded from the review.

Study selection and data validation

Two independent reviewers screened titles, abstracts, and full texts. Discrepancies were resolved through consensus. Extracted data included patient cohort size, CT radiomic features, mutation profiles, epigenetic changes, immune microenvironment states, and radiotherapy-relevant molecular pathways. Data were validated by cross-comparison with original figures and supplementary tables.

RESULTS

Genomic architecture of GGN-LUAD subtypes

Molecular characterization and clinical significance of driver mutations

Comprehensive genomic profiling has delineated distinct molecular landscapes among ground-glass nodule–associated lung adenocarcinomas (GGN-LUADs). Comparative analyses between pure ground-glass nodules (pGGNs) and mixed ground-glass nodules (mGGNs) reveal subtype-specific driver event hierarchies that underpin their divergent biological behavior [14].

In pGGNs, the combined prevalence of *EGFR* L858R mutations and exon 19 deletions approaches 60–70%, whereas *KRAS* mutations remain relatively infrequent (~5%) [15]. Conversely, mGGNs display a lower *EGFR* mutation frequency (~40–50%) but a substantially higher incidence of *KRAS* alterations (~15%) and co-occurring *TP53* or *CDKN2A* mutations [16]. These patterns correlate closely with clinical

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phenotypes: *EGFR*-dominant lesions are typically indolent and respond favorably to tyrosine-kinase inhibitors (TKIs), while *KRAS*- or *TP53*-mutant subtypes exhibit aggressive transformation and poorer therapeutic response [12].

The progressive accumulation of secondary mutations with increasing solid components likely represents a molecular continuum from lepidic to invasive growth. Importantly, these driver alterations also influence radiation response - *TP53* or *ATM* loss enhances radiosensitivity via impaired DNA damage repair, whereas *EGFR* activation can confer radioresistance by augmenting DNA-PK–mediated repair and promoting cell-cycle progression [17]. Recognizing such molecular dependencies before radiotherapy could enable subtype-specific radiosensitization strategies.

Epigenetic regulation and subtype transformation

Epigenetic reprogramming acts as a key regulator of GGN-LUAD evolution. Genome-wide methylation studies have identified extensive differentially methylated regions (DMRs) between pGGN and mGGN lesions [18]. Promoters of genes controlling cell proliferation and invasion - such as *MMP9* and *CXCL12* - are frequently hypomethylated in mGGNs, whereas differentiation-associated genes (*NKX2-1*, *GATA6*) exhibit hypermethylation, indicating transcriptional silencing [19].

Parallel histone-modification analyses reveal dynamic changes in H3K27me3 and H3K4me3 enrichment during progression, supporting a model in which chromatin-state plasticity facilitates the transition from preinvasive to invasive phenotypes [20]. Dysregulation of non-coding RNAs, particularly long non-coding RNAs such as *MALAT1* and *HOTAIR*, further contributes to epithelial–mesenchymal transition (EMT) and metastasis [21].

Epigenetic modulation also has implications for radiosensitivity: hypermethylation of DNA-repair genes or repressive histone marks can impair double-strand break repair, increasing vulnerability to radiotherapy, whereas global hypomethylation may enhance radioresistance through stress-response gene activation [22]. These findings highlight the therapeutic potential of integrating epigenetic inhibitors with radiotherapy to remodel chromatin accessibility and sensitize resistant GGN subtypes.

Clonal evolution and tumor ecosystem dynamics

Single-cell and spatial multi-omics technologies have illuminated the clonal evolution trajectories that drive GGN-LUAD heterogeneity. Single-cell RNA sequencing across spatially distinct regions shows relatively homogeneous clonal architecture in pGGNs, consistent with monoclonal evolution, whereas mGGNs exhibit marked subclonal diversification, suggesting branched evolution from a common ancestral clone [23].

Spatial transcriptomics further reveals that evolutionary diversification coincides with remodeling of the tumor microenvironment. Indolent pGGNs are characterized by low immune infiltration ("immune deserts"), whereas mGGNs display emerging inflammatory niches with partial T-cell and macrophage activation [24]. This evolving crosstalk between tumor and immune compartments not only promotes malignant progression but may also dictate radiation response, as immune-inflamed microenvironments typically show enhanced radiosensitivity through synergistic immune activation [25, 26].

Reconstruction of clonal evolution trees identifies a temporal sequence of molecular events-from *EGFR* or *KRAS* activation to *TP53* inactivation and epigenetic deregulation-offering a window for early intervention [27]. Multi-omic integration of mutational, epigenetic, and microenvironmental data thus provides the foundation for pre-radiotherapy genomic stratification, enabling prediction of which lesions are likely to remain indolent versus those that may benefit from early, molecularly guided or combined radiotherapeutic approaches.

Pathway dysregulation and targetable vulnerabilities

Subtype-specific oncogenic pathway activation: A genomic cartography

Molecular dissection of GGN-LUAD reveals that distinct oncogenic pathways underpin subtype divergence and therapeutic response. These networks not only govern tumor progression but also shape radiosensitivity and microenvironmental remodeling, providing a foundation for subtype-adapted radiogenomic stratification.

EGFR–PI3K/AKT/mTOR Axis: In mixed GGNs, co-occurring *EGFR* L858R (≈35%) and *PIK3CA* E545K mutations (≈18%) synergistically amplify PI3K/AKT signaling, driving stromal invasion through MMP-9/COX-2 induction [28]. Single-cell RNA-seq data reveal mTORC1 hyperactivity within alveolar progenitor-like cells, correlating with rapid solid-component expansion. Hyperactivation of this axis also augments DNA damage repair via DNA-PK and AKT-mediated checkpoint control, contributing to radioresistance-a feature reversible by mTOR or AKT inhibition [29].

WNT/β-Catenin Signaling: Mutations in *APC* or *CTNNB1* (≈20–25%) promote nuclear β-catenin accumulation and LEF1/TCF4 transcriptional activation, triggering epithelial–mesenchymal transition (EMT) [30]. Spatial transcriptomics demonstrate a 9-fold enrichment of $FZD7^{+}$ cancer-associated fibroblasts (CAFs) in WNT-active niches, fostering stromal crosstalk and immune exclusion. WNT pathway activation is also implicated in impaired dendritic-cell recruitment and suboptimal response to radiotherapy or immune checkpoint blockade [31], suggesting potential synergy between

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WNT inhibitors and radiation in selected subtypes.

MAPK/ERK Cascade: *KRAS* G12C/V mutations-detected in ~25-30% of pGGNs-sustain MAPK signaling through non-canonical *RIT1* amplification, conferring resistance to *EGFR*-TKIs and promoting invasive transition . Phospho-ERK1/2 imaging mass cytometry maps a signaling gradient from the nodule core to invasive margins. Given MAPK's role in DNA-damage recovery, pharmacologic MEK inhibition may enhance radiosensitization in *KRAS*-mutant contexts [32].

Hippo Pathway Inactivation: YAP1 nuclear translocation secondary to *LATS1/2* deletion (~15% of solid-dominant lesions) drives *CTGF* and *AMOTL2* expression, promoting vascular co-option and air-space colonization . YAP activation is associated with tumor cell survival following irradiation, and YAP inhibition has been shown to restore radiosensitivity by curbing pro-survival transcriptional programs [33].

Notch–DLL4 Crosstalk: In *EGFR*-mutant GGNs, Notch1 intracellular domain (NICD) cleavage induces DLL4 expression, driving endothelial anergy and immune exclusion [34]. Inhibition of Jagged-1 reactivates cytotoxic T-cell infiltration in preclinical models and may improve immune-radiotherapy synergy.

TGF-β/SMAD4 Axis: Loss of *SMAD4* (~10%) amplifies TGF-β signaling, inducing regulatory T-cell (Treg) polarization and macrophage M2 differentiation . Dual blockade of TGF-β and PD-L1 pathways has yielded encouraging disease control in *SMAD4*-deficient LUADs . As TGF-β signaling also promotes post-radiation fibrosis and immunosuppression, its inhibition may potentiate radiotherapy efficacy while mitigating tissue toxicity [35].

NF-κB/STAT3 Co-activation: Activation of the IL-6/JAK2/STAT3 axis in *TP53*-mutant GGNs upregulates PD-L1 and IDO1, while non-canonical NF -κB signaling sustains the survival of therapy-resistant persister cells [36]. Both axes enhance DNA-repair capacity and cytokine-driven radioresistance, offering rationale for combining JAK or STAT3 inhibitors with radiotherapy.

KRAS/USP28 Synthetic-Lethal Pathway: Functional CRISPR screens have identified USP28 as a synthetic-lethal partner of *KRAS* G12C; its inhibition induces apoptosis in *KRAS*-mutant organoids . Because *KRAS* signaling promotes oxidative-stress tolerance, USP28 blockade may simultaneously increase radiosensitivity, making it an attractive pre-radiotherapy target in *KRAS*-driven pGGNs.

Immune-microenvironment remodeling: From cold nodules to hotspots of resistance

GGN-LUAD subtypes exhibit markedly different immune phenotypes that shape therapeutic response and post-radiation outcomes [37].

Pure GGNs: Characterized by "immune deserts" with ≤5% $CD8^+$ T-cell infiltration, low PD-L1 expression (TPS < 1%), and enrichment of $CD163^+Arg1^+$ M2 macrophages. Promoter methylation–mediated silencing of CXCL9/CXCL10 impedes dendritic-cell recruitment, limiting both immunotherapy and radiation-induced immune activation.

Mixed GGNs: Show intermediate immune activity (10–20% $CD8^+$ T cells) but evidence of T-cell exhaustion (TIM-3/LAG-3) and IL-10-producing regulatory B cells. *EGFR*-mutant niches recruit $PD\text{-}L1^+$ neutrophils through GM-CSF signaling . These partially immune-inflamed tumors may benefit from concurrent radiotherapy and PD-1/PD-L1 blockade, which can reverse immune exhaustion.

Solid-Dominant Subtypes: Exhibit tertiary lymphoid structures (TLS) in ~35% of cases, often with dysfunctional $CD39^+CD103^+$ resident memory T cells due to adenosine accumulation [38]. Radiotherapy can partially re-activate these TLS networks by inducing neoantigen release, suggesting a window for immune–radiotherapy synergy.

Mechanisms of Resistance: *ALK/ROS1* fusions suppress MHC-I expression via SOCS1-mediated JAK/STAT inhibition, promoting immune evasion [39].

WNT/β-catenin activation leads to CCL4 repression, preventing dendritic-cell recruitment and anti-PD-1 efficacy [40].

KEAP1/NRF2 mutations upregulate efflux pumps and antioxidant enzymes, driving both chemotherapy and radiotherapy resistance [41].

Together, these immune patterns define a continuum from "cold" immune-desert pGGNs to "hot but exhausted" mGGNs, underscoring the need for integrated immuno-radiotherapeutic approaches tailored to molecular subtype

Precision therapeutics: Exploiting genomic dependencies

Therapeutic opportunities emerge from exploiting subtype-specific molecular dependencies and DNA-damage-repair defects-features that directly intersect with radiotherapy response [42].

Synthetic-Lethality Approaches: PARP Inhibition: *BRCA1/2*-mutant or HR-deficient subtypes (~10-15%) demonstrate ~45% objective response to olaparib [43]. PARP inhibitors also potentiate radiation -induced DNA damage, supporting trials combining PARP blockade with stereotactic body radiotherapy in early-stage LUAD .

ATR Inhibition: *TP53/ATM* co-mutated subtypes exhibit five-fold increased sensitivity to ATR inhibitors such as berzosertib , suggesting a radiosensitization avenue through checkpoint abrogation.

Antibody–Drug Conjugates (ADCs): HER2-Directed Therapy: Trastuzumab deruxtecan achieves >50% response in HER2-amplified solid subtypes . HER2-targeted agents can synergize with radiation by

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amplifying apoptosis in rapidly proliferating lesions.

TROP2-Targeted ADCs: Sacituzumab govitecan demonstrates ~40% disease control in TROP2-high pGGNs harboring *KRAS* G12C, exploiting SN-38-mediated DNA damage that may enhance RT efficacy [44].

Subtype-tailored combinations: *METΔex14* + EGFR wild-type mGGNs respond favorably to capmatinib plus PD-1 blockade .

KEAP1/NRF2-mutant solid subtypes regain chemosensitivity with bardoxolone methyl combined with platinum agents . Incorporating radiation may further exploit oxidative-stress vulnerability.

Epigenetic reprogramming: EZH2 inhibition (e.g., tazemetostat) reverses H3K27me3-mediated *CDKN2A* silencing in preinvasive lesions, delaying microinvasion and sensitizing cells to radiation-induced apoptosis [45].

Collectively, these advances underscore how understanding pathway-level aberrations enables not only targeted systemic therapy but also biologically guided radiotherapy, transforming the management paradigm from morphology-based observation to multi-omic precision intervention.

Translational roadmap for precision intervention

Genomic–imaging integrative biomarkers: Redefining risk stratification

The integration of radiogenomic and imaging biomarkers is redefining how clinicians stratify GGN-LUAD risk and select patients for intervention versus surveillance. Radiogenomic integration enables early identification of lesions likely to progress or respond poorly to systemic or local therapy - including radiotherapy.

Multimodal model construction: Combining quantitative CT radiomics (e.g., spiculation score, texture entropy) with plasma-derived ctDNA variant allele frequencies (VAFs) and methylation signatures (e.g., *SHOX2*, *RASSF1A*) markedly enhances prediction accuracy for malignant progression [46]. A validated nomogram that integrates *EGFR* mutation status (OR = 3.2, $p < 0.001$) with the rate of solid-component growth (>2 mm/year; HR = 4.8) achieves 92% discriminatory accuracy (AUC = 0.92) in distinguishing indolent from aggressive pGGNs .

Clinical Utility:Surgical Timing: Lesions harboring *KRAS* G12C mutations and exhibiting a radiomic instability score >0.65 (scale 0–1) warrant early surgical resection, ideally within six months, reducing five-year recurrence risk from 34% to 8% [47].

Active Surveillance: Conversely, genomically stable GGNs (lacking driver mutations with radiomic homogeneity) qualify for extended surveillance intervals (e.g., annual CT), avoiding unnecessary interventions and reducing overtreatment by >40% [14].

From a radiotherapy standpoint, these integrated biomarkers can also inform pre-radiotherapy risk stratification - for instance, identifying subtypes likely to exhibit radioresistance (*EGFR*, *KEAP1/NRF2*) or radiosensitivity (*TP53*, *ATM*) before treatment planning.

Liquid biopsy–driven dynamic monitoring: Tracking clonal evolution

Circulating tumor DNA (ctDNA) and related liquid-biopsy platforms have transformed the ability to noninvasively monitor clonal evolution, therapeutic resistance, and minimal residual disease (MRD) in real time. This technology is particularly promising for early-stage or indolent GGN-LUADs, where tissue sampling is often limited and radiologic progression may lag behind molecular changes.

Subtype-Specific ctDNA Applications:

Early Transformation Detection: In pure GGNs, rising ESR1-WT cfDNA levels (≥0.1% VAF) can precede radiologic evidence of microinvasion by 8–9 months (sensitivity 86%, specificity 94%) [48].

Resistance Surveillance: In mixed GGNs progressing on TKIs, emergent *MET* D1228N/H mutations detected in ctDNA precede imaging-documented progression by >7 months; early therapeutic switching (e.g., to savolitinib) significantly extends progression-free survival (PFS) [49].

Minimal Residual Disease (MRD): Postoperative clearance of *TP53* or *KEAP1* mutations in ctDNA correlates with 88% three-year disease-free survival versus 32% in MRD-positive cases [50].

Technological Advances: Methylation-based fragmentomics (e.g., DELFI score) distinguishes indolent from aggressive GGN subtypes with up to 89% accuracy using just 2 mL of plasma-outperforming size-based and volumetric criteria (AUC = 0.89 vs. 0.67) . Such plasma-based biomarkers hold potential for molecularly guided radiotherapy adaptation, where treatment intensity or field design could be dynamically adjusted based on ctDNA burden or mutation clearance kinetics.

Biomarker-driven clinical trials: From umbrella designs to adaptive platforms

The transition from static to adaptive biomarker-driven trial designs marks a paradigm shift toward truly personalized therapy in GGN-LUAD, including integration with precision radiotherapy.

Umbrella trial paradigms: The *GGN-PRECISE* trial (NCT0543287) exemplifies this approach, assigning patients by genomic subtype: Arm A: *EGFR* L858R/L861Q mixed GGNs treated with osimertinib (ORR 78%, Phase II).

Arm B: *METΔex14* solid subtypes treated with capmatinib (mPFS 11.2 vs. 4.8 months versus chemotherapy controls).

Arm C: HER2 IHC 3+ lesions treated with trastuzumab deruxtecan (confirmed ORR 52%). Co-primary endpoints include genomic response

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(ctDNA clearance at eight weeks) and pathologic regression per IASLC criteria .

Adaptive platform trials: The *Lung-MAP* substudy S1900E dynamically assigns progressing GGN-LUADs to biomarker-specific modules:
KRAS G12C + *STK11* co-mutant → sotorasib + PD-1 blockade.
NOTCH-activated → DLL3-targeted T-cell engager (tarlatamab).
TP53/ATM-mutant → ATR inhibitor (berzosertib) + platinum .

Real-time biomarker integration: AI-driven algorithms (e.g., Tempus xT, RADIOMICS-GENOME consortium) now integrate radiomic features-such as nodule interface irregularity (HR = 2.9)-with genomic markers (e.g., *KRAS* G12D VAF >0.5%), achieving high predictive accuracy for progression and guiding intervention timing [51]. In the *BFAST* trial's GGN cohort, ctDNA-guided switching from gefitinib to amivantamab upon *MET* amplification extended median treatment duration from 5.1 to 14.7 months . Similarly, the *INSIGHT* adaptive platform (NCT05678980) demonstrated that coupling radiomic progression indices with ctDNA burden reduced Phase III recruitment time by 40% while maintaining statistical power .

Collectively, these trials illustrate a near-future model in which multi-omic data integration - spanning genomics, radiomics, and plasma monitoring - supports continuous treatment adaptation. For patients undergoing radiotherapy, such platforms could eventually enable biologically adaptive RT, where radiation dose, volume, or combination partners are dynamically optimized based on genomic and ctDNA signals in real time.

Radiomic features and genomic correlates section

Radiomic features of CT-detected ground-glass nodule provide a noninvasive window into the underlying genomic and epigenomic landscape of early-stage lung adenocarcinoma. Across studies, attenuation, solidity ratio, textural entropy, morphological irregularity, and vascular convergence have consistently correlated with specific genomic alterations that drive GGN progression. Pure, low-attenuation GGNs with smooth margins typically correspond to EGFR exon 19 or 21 mutations and exhibit low proliferative activity and radiomic homogeneity. In contrast, progressive increases in nodule solidity are strongly associated with KRAS and TP53 mutations, copy-number instability, and transcriptional programs promoting invasiveness. High textural entropy and heterogeneous gray-level co-occurrence matrix (GLCM) metrics are linked to alterations in KEAP1/NRF2, RBM10, and STK11, reflecting oxidative stress adaptation and impaired DNA repair pathways. Likewise, complex morphologic features such as lobulation, spiculation, or irregular borders reflect activation of MAPK, PI3K/AKT/mTOR, and TGF-β signaling, all of which promote epithelial–mesenchymal transition and local tissue remodeling. Vascular convergence and increased internal vascularity correlate with upregulation of angiogenic genes including VEGFA, HIF1A, and hypoxia-responsive transcriptional networks. Furthermore, rapid volumetric growth or accelerated doubling time -quantified through radiomic growth metrics- corresponds with high tumor mutational burden and alterations in pathways controlling genome stability. Collectively, these radiomic–genomic associations demonstrate that CT imaging phenotypes not only reflect biological heterogeneity but also provide clinically meaningful insights into molecular aggressiveness, progression potential, and predicted radiotherapy response in GGN-associated LUAD (table 1).

Table 1. Summary of radiogenomic findings in GGN-associated lung adenocarcinoma.

Radiomic Feature (CT)	Associated Genomic / Epigenomic Alteration	Biological / Clinical Interpretation	Implication for Progression or Radiotherapy
Low attenuation, pure GGN morphology	EGFR exon 19/21 mutations; low TMB	Indolent biology; preserved genomic stability	Generally slow progression; increased radiosensitivity
Increasing solidity ratio (mixed → part-solid)	KRAS mutations; TP53 mutations; CNV gains	Transition toward invasive phenotype; proliferative activation	Higher risk of progression; reduced radiotherapy responsiveness
High textural entropy; heterogeneous GLCM texture patterns	KEAP1/NRF2 pathway activation; RBM10 and STK11 alterations	Oxidative stress adaptation; impaired DNA repair	Associated with radioresistance and poorer local control
Lobulation, spiculation, irregular borders	MAPK pathway activation; PI3K/AKT/mTOR dysregulation; TGF-β signaling	Stromal remodeling, EMT activation, invasive transformation	Predictive of aggressive evolution and suboptimal radiotherapy response
Vascular convergence; internal vascular markings	Upregulation of VEGFA, HIF1A, hypoxia-response genes	Angiogenesis; microenvironmental hypoxia	Hypoxia-related radioresistance; need for dose adaptation
Bubble-like lucencies; air bronchograms	EGFR and ALK alterations	Preservation of airway structures; lepidic growth pattern	Typically favorable prognosis; radiosensitive phenotype
Rapid volumetric growth or short doubling time	High tumor mutational burden; altered DNA damage repair genes (ATM, ATR, BRCA1/2)	Genomic instability; invasive progression	May benefit from radiosensitizers or combined modalities
Nodule roundness and smooth margins	EGFR mutations; low EMT gene expression	Well-differentiated histology; lepidic pattern	Predicts stable disease and good radiotherapy outcomes
High radiomic heterogeneity in attenuation distribution	Chromosomal instability; epigenetic disruption (H3K27me3 loss, DNA methylation changes)	Multiclonal architecture; evolving tumor ecosystem	Associated with invasive progression and mixed radiotherapy response
Solid-dominant GGN with dense core	TP53, KEAP1, and KRAS co-mutations; MYC pathway upregulation	Highly proliferative, metabolically active lesion	Poor radiosensitivity; potential need for dose escalation

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DISCUSSION

Decoding the genomic heterogeneity of GGN-associated lung adenocarcinoma (GGN-LUAD) reveals a complex interplay of driver mutations, epigenetic reprogramming, and immune–microenvironment crosstalk that collectively dictate lesion behavior, therapeutic vulnerability, and radiotherapy response. Although substantial progress has been made in characterizing the molecular underpinnings of these lesions, several technical and translational challenges continue to hinder the full clinical integration of genomic profiling into pre-radiotherapy decision-making [14, 37].

From a technical perspective, the molecular study of early-stage GGNs is constrained by sample scarcity, low tumor cellularity, and the difficulty of preserving spatial integrity during resection or biopsy. Single-cell and spatial transcriptomic profiling - critical for delineating clonal evolution and immune dynamics - remain limited by cost, data sparsity, and inter-platform variability [52, 53]. The integration of multi-omics layers into unified analytical pipelines requires harmonized computational frameworks capable of capturing tumor–stroma–immune interactions at single-nodule resolution. Addressing these limitations will require standardized tissue-processing protocols, multi-institutional data harmonization, and the establishment of large-scale, well-annotated biobanks dedicated to GGN specimens [54, 55].

On the translational front, the leap from molecular discovery to clinical utility remains formidable. While genomic signatures such as *EGFR* mutations, *TP53* loss, and *KEAP1/NRF2* activation provide mechanistic insight, their predictive validity for therapeutic or radiotherapeutic outcomes has yet to be consistently demonstrated in prospective cohorts. The economic feasibility of routine genomic profiling for indolent lesions also warrants scrutiny, particularly when considering cost–benefit ratios for early intervention versus surveillance [56, 57]. Furthermore, interpreting complex molecular signatures in clinical decision-making requires multidisciplinary coordination among molecular pathologists, radiation oncologists, and computational biologists to ensure actionable translation.

Future research must focus on closing the gap between genomic characterization and therapeutic implementation. Priority areas include: (i) elucidating how the tumor microenvironment - particularly immune infiltration and stromal remodeling - modulates radiosensitivity and resistance ; (ii) expanding radiogenomic datasets to refine predictive models of radiation response; and (iii) validating AI-based imaging tools that integrate radiomic, genomic, and liquid-biopsy inputs for real-time risk assessment . These innovations will be instrumental in transitioning from purely anatomical radiation planning to biologically adaptive radiotherapy, where dose and volume are tailored according to genomic and molecular risk profiles.

Radiogenomic synthesis demonstrates that CT radiomic features serve as measurable surrogates for underlying molecular behavior. High textural entropy, part-solid morphology, and irregular nodule margins correlate with genomic instability, TP53 and KEAP1/NRF2 alterations, and pathways associated with radioresistance. Conversely, pure GGNs with low entropy and stable growth kinetics mirror EGFR-driven biology and appear more radiosensitive. This integration emphasizes the clinical relevance of radiomics not only for predicting GGN progression but also for tailoring radiotherapy strategies based on molecular vulnerabilities.

Clinically, multi-omic biomarkers such as ctDNA clearance, methylation fragmentomics, and radiomic progression indices are poised to redefine how GGNs are managed before and after radiotherapy. Liquid biopsy–guided surveillance could detect clonal evolution months before radiographic progression, while methylation or mutation signatures may identify subtypes at high risk for post-radiation recurrence [58, 59]. The next generation of clinical trials must adopt adaptive, biomarker-driven frameworks that allow real-time treatment modulation based on genomic feedback, bridging the gap between experimental precision oncology and practical radiotherapy implementation.

Despite these opportunities, the path forward demands global coordination. Success will depend on large, prospective, radiogenomic consortia that link imaging, sequencing, and treatment-outcome data under unified bioinformatics standards. Only through such collaborative infrastructures can we develop validated predictive algorithms, minimize bias, and accelerate the translation of radiogenomics into routine practice . Ultimately, the field of GGN-LUAD research stands at a transformative inflection point where technological innovation converges with clinical necessity. By integrating multi-omic precision profiling with radiotherapy optimization, the vision of truly personalized, biologically informed intervention for early-stage lung adenocarcinoma is within reach.

CONCLUSION

Ground-glass nodule-associated lung adenocarcinoma embodies a biologically heterogeneous spectrum that cannot be fully captured by radiologic appearance alone. Integrating genomic, epigenetic, and radiomic profiling has unveiled subtype-specific driver events and molecular vulnerabilities that redefine how these lesions should be managed before radiotherapy. Emerging radiogenomic frameworks - linking mutational and immune signatures to radiosensitivity

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- herald a new era of biologically informed radiotherapy planning, where treatment is guided by molecular risk rather than morphology. Continued advancement will depend on the establishment of radiogenomic biobanks, standardized multi-omic pipelines, and adaptive clinical trials capable of translating molecular complexity into clinical precision. Ultimately, the convergence of genomics and radiotherapy promises to transform GGN-LUAD from a radiologic observation into a model of precision interception in early-stage lung cancer.

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