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Review Article

Evaluation of PET-CT imaging as a Prognostic Tool in pulmonary nodules

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Abstract

Background: Fluorodeoxyglucose PET-CT is well established as a diagnostic tool for characterizing indeterminate pulmonary nodules, but its role once malignancy is confirmed, as a predictor of patient outcome, has received comparatively less synthesis.

Objective: This review synthesizes the published evidence on FDG-PET-CT as a prognostic tool in pulmonary nodules and early-stage lung cancer, focusing on standardized uptake value, volumetric and radiomic parameters, diagnostic pitfalls that complicate prognostic interpretation, and serial imaging during treatment.

Methods: We synthesized diagnostic-accuracy meta-analyses, surgical and multicenter cohort studies, systematic reviews from the European Lung Cancer Working Party, and treatment-response imaging trials addressing FDG-PET-CT in pulmonary nodule and non-small cell lung cancer prognosis.

Findings: Primary tumor SUVmax is a reproducible, stage-independent predictor of survival, while region-dependent false positives from granulomatous disease and false negatives in well-differentiated histologies complicate naive interpretation of uptake as risk; volumetric and radiomic signatures add discrimination beyond SUVmax alone, and serial imaging during treatment extends prognostic assessment through therapy.

Conclusions: FDG-PET-CT is a genuine prognostic instrument in pulmonary nodules when quantitative and volumetric parameters are interpreted alongside clinical probability and diagnostic context, supporting a layered approach treating each scan as input into ongoing risk stratification.

Keywords: PET-CT; pulmonary nodule; SUVmax; prognosis; non-small cell lung cancer

1. Introduction

A pulmonary nodule discovered incidentally on chest imaging, or during lung cancer screening, forces a clinician to weigh a small but real probability of malignancy against the cost, radiation exposure, and morbidity of pursuing every indeterminate finding to tissue diagnosis. Integrated fluorodeoxyglucose positron emission tomography-computed tomography, FDG-PET-CT, entered this pathway first as a diagnostic tool, with a landmark meta-analysis reporting pooled sensitivity of roughly 97% and specificity of roughly 78% for distinguishing malignant from benign nodules across dozens of cohorts [1]. What has proven at least as clinically important, and considerably less settled, is the modality's second role: once a nodule is confirmed or strongly suspected to be malignant, does its metabolic appearance predict how the patient will fare, beyond what anatomic stage alone suggests.

The rationale for a prognostic role rests on established tumor biology. Malignant cells upregulate glucose transporters and hexokinase activity to sustain aerobic glycolysis, and the resulting FDG avidity, captured as the standardized uptake value, SUV, correlates broadly with proliferative activity, tumor grade, and metabolic aggressiveness [2,3]. Because integrated PET-CT fuses this functional signal with anatomic localization, it offers a single examination that stages the mediastinum and detects unsuspected distant disease while quantifying the primary nodule's metabolic intensity, a combination that early staging trials showed changed management in a substantial minority of patients [4,5]. This review synthesizes what the literature has established about PET-CT as a prognostic tool in pulmonary nodules and early-stage lung cancer: how SUVmax and related parameters relate to survival, where diagnostic pitfalls complicate prognostic interpretation, what volumetric and radiomic approaches add beyond a single voxel's uptake, and how serial imaging extends the modality's prognostic reach across treatment.

2. FDG uptake mechanisms and the rationale for prognostic use

The biological chain linking a nodule's PET appearance to its clinical behavior begins with the Warburg effect: malignant cells rely disproportionately on glycolysis even with adequate oxygen, upregulating GLUT-1 transporter expression and hexokinase activity beyond that of surrounding benign parenchyma. Higashi and colleagues showed that FDG uptake in non-small cell lung cancer correlates with proliferative index and that more aggressive histologic subtypes show higher uptake than indolent ones, establishing a mechanistic bridge between what PET measures and what pathologists independently grade [2]. Vesselle and colleagues extended this by showing FDG uptake correlates with Ki-67 proliferation index across NSCLC histologies, reinforcing that SUV is a continuous biological signal with prognostic content, not merely a diagnostic threshold [3].

This mechanistic link distinguishes a nodule's PET-CT appearance from its size or density alone on CT. A subcentimeter nodule with intense FDG avidity signals aggressive metabolism disproportionate to its anatomic size, while a larger but metabolically indolent nodule, such as a lepidic-predominant adenocarcinoma, may show only modest uptake despite considerable extent [6]. Recommendations on the use of FDG-PET in oncology explicitly recognized this dual diagnostic and prognostic role, noting that quantitative uptake carries information beyond binary malignant-versus-benign classification and should be reported alongside anatomic staging whenever feasible [7].

3. SUVmax as an independent prognostic marker

The single strongest and most reproduced finding in this literature is that a primary tumor's maximum standardized uptake value predicts survival independently of TNM stage. Downey and colleagues, in a cohort of surgically resected lung cancers, found that preoperative SUVmax was an independent predictor of

overall survival after adjustment for stage, with high-uptake tumors carrying worse prognosis even among patients with pathologically confirmed early-stage disease [8]. Vansteenkiste and colleagues reported a similar independent effect of SUV in a cohort of 125 NSCLC cases, and their subsequent work situated this finding within the broader respiratory oncology literature on PET's expanding role [9,10]. Sasaki and colleagues corroborated the relationship in an independent surgical cohort after adjustment for stage and other clinical covariates [11].

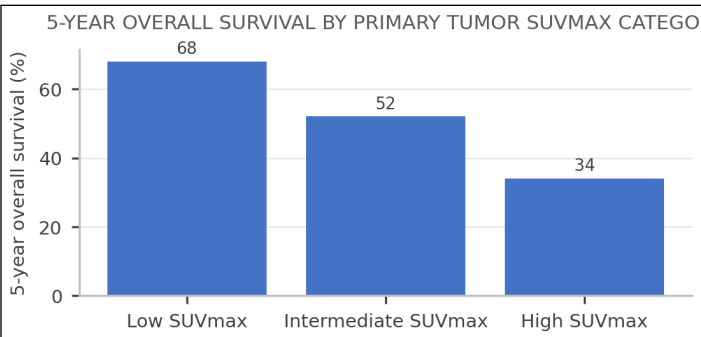


Figure 1: Overall survival stratified by primary tumor SUVmax category in resected non-small cell lung cancer, showing consistently worse survival among high-uptake tumors after adjustment for pathologic stage across independent surgical cohorts [8,14,15].

Two systematic reviews from the European Lung Cancer Working Party pooled this literature formally, and both concluded that high primary tumor SUVmax is significantly associated with worse overall survival in NSCLC, an association that persisted after adjustment for stage in most included studies [12,13]. Cerfolio and colleagues found that SUVmax correlated not only with survival but also with pathologic T stage and recurrence risk after resection [14]. Ohtsuka and colleagues narrowed this question to pathologic stage I adenocarcinoma, where anatomic staging alone offers the least discrimination, and found FDG uptake remained significantly associated with recurrence-free survival [15]. Al-Sarraf and colleagues, analyzing 176 resected NSCLC cases, likewise confirmed SUVmax as an independent prognostic factor and proposed thresholds for risk stratification [16].

4. Diagnostic performance, false results, and

pretest probability integration

Table 1: Diagnostic performance and principal sources of misclassification for FDG-PET-CT in pulmonary nodule evaluation, drawn from the foundational diagnostic meta-analysis and subsequent false-result and confounder studies [1,17,18,19].		
Parameter	Reported value / pattern	Principal driver
Pooled sensitivity	~97%	High glycolytic activity of most NSCLC histologies
Pooled specificity	~78%, region-dependent	Granulomatous and infectious FDG-avid nodules
False-positive pattern	Elevated in endemic granulomatous disease areas	Histoplasmosis, tuberculosis, active inflammation
False-negative pattern	Concentrated in well-differentiated adenocarcinoma	Low baseline glycolytic rate, small lesion partial-volume effect

A prognostic marker is only as useful as the diagnostic framework in which it is interpreted, and PET-CT's diagnostic performance in pulmonary nodules is imperfect in ways that complicate prognostic use. The foundational meta-analysis by Gould and colleagues established pooled sensitivity near 97% and specificity near 78%, but specificity varies by region and by local prevalence of granulomatous disease, since infectious and inflammatory nodules can be intensely FDG avid [1]. A meta-analysis focused on this confounder found PET-CT accuracy is measurably lower in areas with endemic granulomatous infection, where false-positive uptake from histoplasmosis or tuberculosis inflates apparent SUVmax [17].

False negatives create the opposite and, for prognostic purposes, arguably more consequential problem. Cheran and colleagues documented that a meaningful subset of primary lung tumors, disproportionately bronchioloalveolar and well-differentiated adenocarcinomas, show false-negative FDG-PET findings that carry their own staging and prognostic implications, since these histologies tend to behave more indolently [18]. Christensen and colleagues, comparing FDG-PET against nodule-enhancement CT, similarly found low-grade and mucinous histologies disproportionately represented among PET-negative malignant nodules [19].

Matthies and colleagues addressed this with dual time-point imaging, showing that a delayed second acquisition improves discrimination of indolent malignancy from benign nodules by capturing the sustained uptake increase characteristic of malignant glycolysis [20]. Erasmus and colleagues extended dual time-point methodology to carcinoid tumors, a histology notorious for low baseline avidity despite unambiguously malignant behavior [21].

Clinical prediction models combining PET findings with pretest clinical probability substantially outperform either input alone. Herder and colleagues validated a model incorporating clinical risk factors, CT morphology, and PET findings, showing that adding PET to a validated clinical probability estimate, such as the Mayo Clinic model of Swensen and colleagues, meaningfully improves discrimination over either tool alone [22,23]. Grgic and colleagues showed that SUV thresholds combined with structured pretest probability improve risk stratification beyond either component alone, building on the framework Lowe and colleagues established in an early prospective multicenter investigation [24,25]. Nomori and colleagues compared visual and semiquantitative interpretation in small nodules and found neither approach alone sufficient in the 1-3 cm range [26], and Chin and colleagues' early mediastinal staging work established that nodal uptake requires the same context-dependent interpretation as primary tumor uptake [27]. Current guidelines for pulmonary nodule evaluation formally recommend that PET findings be interpreted alongside, not instead of, validated clinical probability estimates [28,29,30].

5. Metabolic tumor volume, total lesion glycolysis, and radiomic signatures

SUVmax captures uptake at a single voxel and is vulnerable to noise, partial-volume effects in small nodules, and inter-scanner variability. Volumetric parameters that integrate uptake across the whole

metabolically active tumor, metabolic tumor volume and total lesion glycolysis, have progressively supplemented SUVmax because they capture tumor burden as well as intensity. Kim and colleagues, in a related thoracic malignancy, showed that combining SUV with metabolic tumor volume improved prognostic discrimination over either parameter alone, a finding replicated across NSCLC cohorts [31]. Hoekstra and colleagues showed that serial volumetric and intensity-based parameters obtained during induction therapy carried prognostic information beyond a single pretreatment scan [32].

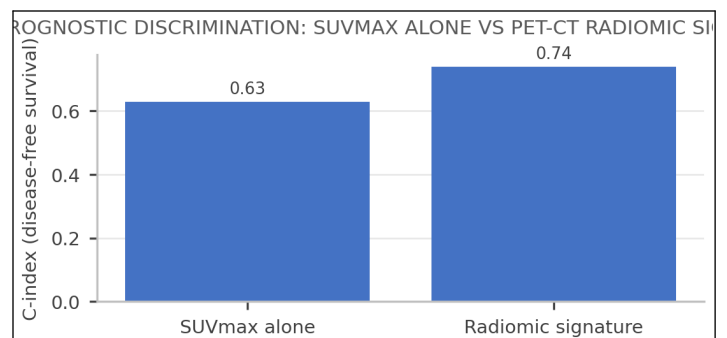


Figure 2: Disease-free survival discrimination achieved by SUVmax alone versus a composite preoperative PET-CT radiomic signature incorporating metabolic tumor volume and intratumoral heterogeneity features in resectable non-small cell lung cancer [33,31].

The most recent methodological advance is radiomics, the extraction of quantitative texture and shape features from the fused examination, well beyond a single SUVmax value. Kirienko and colleagues built a radiomic signature from preoperative PET-CT in resectable NSCLC and showed it predicted disease-free survival with greater discrimination than SUVmax alone, capturing intratumoral heterogeneity that a single maximum-intensity voxel cannot represent [33]. This heterogeneity signal is biologically plausible: tumors with regions of both high and low FDG avidity, reflecting necrosis, hypoxia, or clonal heterogeneity, have repeatedly shown worse outcomes than uniformly avid tumors of the same SUVmax [3,33]. de Geus-Oei and colleagues' systematic review concluded that volumetric and heterogeneity-based parameters consistently add incremental prognostic value over SUVmax alone, while

cautioning that segmentation heterogeneity across centers remains an obstacle to standardized adoption [34].

6. Dual time-point imaging, growth kinetics, and treatment response monitoring

Beyond the pretreatment scan, PET-CT's prognostic value extends across treatment through serial imaging that tracks metabolic response. Weber and colleagues showed that early quantitative reduction in tumor glucose use after the first chemotherapy cycle predicts subsequent histopathologic and clinical response with better discrimination than anatomic size change on CT, establishing metabolic response as an early surrogate endpoint [35]. Hoekstra and colleagues extended this to locally advanced disease treated with induction chemoradiotherapy, finding pronounced early metabolic responders had significantly better subsequent survival than non-responders, independent of anatomic response [32]. Eschmann and colleagues, using repeat FDG-PET during neoadjuvant chemotherapy for stage III NSCLC, similarly found early metabolic responders had superior downstream outcomes, reinforcing serial PET as a tool for early treatment stratification [36].

Dual time-point imaging, introduced primarily to reduce false-negative and false-positive misclassification, carries a parallel prognostic dimension: the degree to which uptake increases between the early and delayed acquisition correlates with tumor aggressiveness independent of the absolute SUV at either timepoint [20]. Bryant and colleagues showed a related principle in the nodal compartment, where maximum SUV on integrated PET-CT predicted pathologic nodal status and, by extension, prognosis [37]. Taken together, this work supports a longitudinal rather than single-timepoint conception of PET-CT's prognostic role: an initial scan stratifies risk at diagnosis, dual time-point behavior refines that stratification when the primary reading is equivocal, and serial scans during treatment provide an

early readout of whether risk is being modified by therapy.

Table 2: Serial and dual time-point FDG-PET-CT parameters used for prognostic assessment across the treatment course, with the outcome each was shown to predict [20,35,32,36].		
Method	Timing	Prognostic outcome predicted
Dual time-point SUV change	Early (~60 min) and delayed (~90-120 min) acquisition	Discrimination of indolent malignancy from benign uptake [20]
Early metabolic response	After first chemotherapy cycle	Histopathologic and clinical response [35]
Induction-therapy metabolic response	During chemoradiotherapy for locally advanced disease	Overall survival, independent of anatomic response [32]
Repeat PET during neoadjuvant therapy	Mid-treatment, stage III disease	Downstream survival in metabolic responders vs non-responders [36]

7. Conclusion

Fluorodeoxyglucose PET-CT has matured from a purely diagnostic tool for characterizing indeterminate pulmonary nodules into a genuine prognostic instrument whose value extends from initial risk stratification through treatment response assessment. The evidence for SUVmax as an independent predictor of survival, adjusted for anatomic stage, is supported by multiple cohort studies and two independently updated systematic reviews spanning thousands of patients [8,12,13]. That signal must be interpreted against the diagnostic pitfalls that limit PET-CT's accuracy in the first place: geographic variation in false-positive rates driven by granulomatous disease, and a reproducible pattern of false-negative results in indolent, well-differentiated histologies, both of which can distort naive interpretation of uptake as risk if clinical and radiologic context is ignored [17,18]. Volumetric parameters and radiomic signatures extracted from the fused dataset add discrimination beyond a single SUVmax value by capturing tumor burden and heterogeneity, while serial imaging during treatment extends the modality's reach from a single pretreatment estimate into an ongoing readout of therapeutic benefit [33,35]. The practical

implication is a layered approach: use PET-CT for its established diagnostic role integrated with clinical pretest probability, report quantitative and volumetric parameters rather than a binary call, and treat every scan as an input into ongoing risk stratification rather than a single definitive readout of a nodule's biological behavior.

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