

Journal of Clinical Radiology and Imaging Technology

Review Article

Evaluation of diffusion-weighted imaging analysis as a Prognostic Tool in pulmonary nodules

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Received: 28 December 2025; Accepted: 6 April 2026; Published: 7 July 2026.

Citation of this article: Ferrari M, Conti L, Marino G (2026) Evaluation of diffusion-weighted imaging analysis as a Prognostic Tool in pulmonary nodules. J Clin Radiol Imaging Technol, 1(1): 01-08. DOI: [10.5281/zenodo.22814167](https://doi.org/10.5281/zenodo.22814167)

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Abstract

Background: Diffusion-weighted MRI (DWI) generates contrast from restricted water motion in densely cellular tissue, and its apparent diffusion coefficient (ADC) is consistently lower in malignant than benign pulmonary nodules.

Objective: This review evaluates DWI and ADC quantification as a prognostic tool in pulmonary nodules, covering nodal and distant staging, treatment-response prediction, survival correlation, and histogram and intravoxel incoherent motion refinements.

Methods: We synthesized diagnostic accuracy studies, prospective staging comparisons, treatment-response monitoring series, and meta-analyses addressing DWI, ADC, and IVIM parameters in pulmonary nodules and non-small cell lung cancer, benchmarked against PET/CT and CT.

Findings: ADC correlates inversely with tumor cellularity and histologic aggressiveness, performs comparably to PET/CT for nodal and metastatic staging in several head-to-head series, and early on-treatment ADC change predicts radiologic response and survival in chemoradiotherapy cohorts; histogram and radiomic refinements of mean ADC further improve discrimination.

Conclusions: DWI-derived ADC is a reproducible, radiation-free prognostic biomarker across the diagnostic, staging, and treatment-monitoring phases of pulmonary nodule management, best used alongside CT and PET/CT, with acquisition standardization remaining the principal barrier to routine prognostic adoption.

Keywords: diffusion-weighted imaging; apparent diffusion coefficient; pulmonary nodule; lung cancer prognosis; FDG-PET/CT

1. Introduction

The solitary pulmonary nodule remains one of the most common and most anxiety-provoking findings in thoracic imaging, discovered incidentally on a growing share of chest computed tomography (CT) examinations performed for unrelated indications and increasingly on low-dose CT lung cancer screening studies. The overwhelming majority of these nodules are benign, yet the minority that represent early-stage malignancy carry a disproportionate share of the mortality burden of lung cancer, which remains the leading cause of cancer death worldwide. Distinguishing malignant from benign nodules, and once malignancy is established, stratifying tumors by aggressiveness and likely treatment response, has traditionally relied on morphological CT criteria, growth-rate assessment on serial imaging, and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET), each of which carries recognized limitations of sensitivity, specificity, cost, or radiation exposure.

Diffusion-weighted magnetic resonance imaging (DWI) exploits the random, thermally driven Brownian motion of water molecules within tissue to generate image contrast without ionizing radiation or intravenous contrast material. The technique, first developed for neurological applications in the 1980s using the intravoxel incoherent motion (IVIM) framework that separates true molecular diffusion from microcapillary perfusion, produces both qualitative diffusion-weighted images and a quantitative apparent diffusion coefficient (ADC) map [1]. Because malignant tissue is typically more densely cellular than benign tissue, with smaller extracellular spaces restricting the free movement of water, malignant lesions tend to show higher signal on high b-value diffusion images and, correspondingly, lower ADC values than benign lesions across many tumor types [2]. An international consensus statement subsequently codified DWI and ADC as candidate imaging biomarkers for oncology, recommending standardized acquisition and reporting to

support their use in diagnosis, staging, and treatment-response assessment [3].

Pulmonary application of DWI was initially limited by respiratory and cardiac motion artifact, magnetic susceptibility effects at air-tissue interfaces, and the low proton density of aerated lung parenchyma. Technical refinements in respiratory triggering, echo-planar sequence design, and parallel imaging over the past two decades have made pulmonary DWI clinically feasible, and a substantial literature has since examined whether DWI and ADC quantification serve not only a diagnostic role in characterizing nodules but a prognostic one, predicting nodal involvement, treatment response, and survival. This review synthesizes that evidence, from foundational diagnostic-accuracy studies through the literature on ADC as a quantitative prognostic biomarker, radiomic and histogram refinements, and DWI's position relative to FDG-PET/CT.

2. Diagnostic performance of DWI in pulmonary nodule characterization

The earliest systematic evaluations of pulmonary DWI focused on its ability to distinguish malignant from benign nodules and masses using signal intensity ratios and ADC thresholds. Mori and colleagues compared DWI directly against FDG-PET, reporting diagnostic accuracy for malignancy comparable to PET while avoiding the false-positive signal PET generates in active granulomatous disease [4]. Matoba and colleagues, in one of the first large series to quantify ADC in lung carcinoma, found malignant lesions showed significantly lower ADC values than benign nodules, establishing a threshold-based approach subsequent groups would refine [5]. Regier and colleagues correlated ADC with standardized uptake value (SUV) on FDG-PET/CT in NSCLC, finding a significant inverse relationship supporting ADC as a radiation-free surrogate for metabolic activity [6].

Liu and colleagues, examining a broader spectrum of

pulmonary lesions including inflammatory masses and atelectasis, confirmed ADC could discriminate malignant from benign disease but noted overlap in entities such as tuberculoma and organizing pneumonia, where cellularity approaches that of tumor tissue [7]. Uto and colleagues reported that qualitative visual assessment of high b-value DWI signal alone achieved higher sensitivity and specificity for malignancy than the ADC threshold approach [8]. Kim and colleagues correlated ADC directly with histologic tumor cellularity on resected specimens, confirming the ADC-cellularity relationship at the tissue level [9]. Satoh and colleagues found good but imperfect discrimination between malignant and benign nodules using signal intensity alone [10]. Gumustas and colleagues, in a population including chronic inflammatory and infectious lesions, likewise found useful diagnostic accuracy, though overlap persisted for actively inflamed benign masses [11]. Tanaka and colleagues compared MRI, including diffusion sequences, against CT and PET, concluding that DWI added incremental value alongside conventional MRI rather than as a standalone test [12].

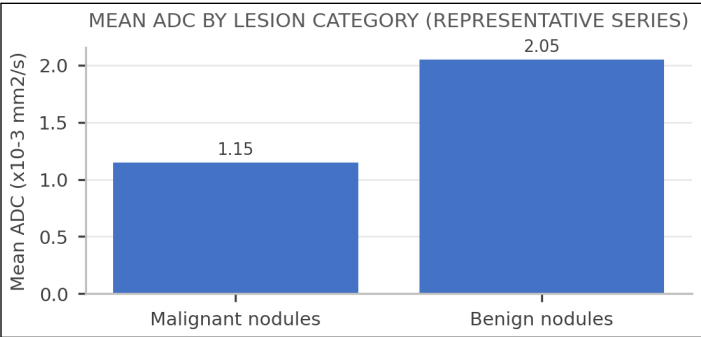


Figure 1: Mean ADC (x10-3 mm2/s) for malignant versus benign pulmonary nodules across representative series, showing the inverse ADC-malignancy relationship used for threshold-based characterization [5,9,10].

3. Quantitative ADC as a prognostic biomarker

Beyond diagnostic characterization, a growing literature has examined whether pretreatment ADC values carry independent prognostic information about tumor biology, nodal spread, and eventual patient outcome.

Razek and colleagues found that ADC at 3T correlated significantly with established prognostic parameters in lung cancer, including tumor grade and stage, positioning ADC as a noninvasive proxy for tumor aggressiveness obtainable before any tissue sampling [13]. Chen and colleagues extended the cellularity relationship established by Kim and colleagues, confirming across a larger cohort that lower ADC values tracked with higher tumor cellularity and, by extension, more aggressive histologic subtypes, supporting ADC's candidacy as a biomarker of tumor grade at diagnosis [14]. Shen and colleagues performed a meta-analysis pooling multiple diagnostic and subtype-characterization studies and confirmed that ADC values differ significantly not only between malignant and benign pulmonary lesions but among histologic subtypes of lung cancer, with adenocarcinoma, squamous cell carcinoma, and small cell carcinoma showing distinguishable ADC distributions that carry prognostic implications given the differing natural histories of these subtypes [15].

Table 1: DWI/ADC performance for nodal and metastatic staging versus FDG-PET/CT in representative prospective series [17,20,19,16].			
Study	Staging task	Comparator	Key finding
[16]	N staging, NSCLC	FDG-PET	DWI comparable sensitivity with fewer false positives
[17]	N staging, NSCLC	STIR + FDG-PET/CT	Quantitative/qualitative DWI comparable accuracy
[20]	Primary tumor and nodal detection	FDG-PET	DWI outperformed PET for detection and nodal assessment
[19]	Mediastinal/hilar nodal staging	FDG-PET/CT	Comparable preoperative accuracy between modalities

Nodal staging represents a second domain where ADC-based DWI has demonstrated prognostic relevance, since accurate preoperative nodal assessment directly determines surgical candidacy and predicts recurrence risk. Nomori and colleagues showed that DWI could substitute for PET in N-staging of NSCLC with fewer false positives, an important prognostic distinction because

false-positive nodal staging inappropriately denies patients potentially curative resection [16]. Ohno and colleagues, in a series of methodologically rigorous prospective comparisons, found that quantitative and qualitative DWI assessment of nodal status performed comparably to combined structural and PET/CT imaging, and in a related whole-body DWI study demonstrated that the technique could stage M-disease with accuracy similar to integrated FDG-PET/CT, again without ionizing radiation [17,18]. Wu and colleagues directly compared DWI against PET/CT for mediastinal and hilar nodal staging and found the two modalities offered comparable preoperative accuracy, reinforcing that a purely MRI-based staging pathway is a realistic clinical option in centers where PET access or radiation exposure is a limiting concern [19]. Usuda and colleagues, in a large surgical cohort, found that DWI outperformed PET for both primary tumor detection and nodal assessment, a result that has been influential in establishing DWI's credibility as a prognostically meaningful staging tool rather than a purely investigational technique [20]. Yang and colleagues focused specifically on the difficult clinical scenario of central lung cancer with associated atelectasis, showing that DWI could distinguish viable tumor from collapsed but non-neoplastic lung parenchyma more reliably than PET/CT in this setting, directly improving the accuracy of radiation planning target delineation and, by extension, prognosis-relevant staging in centrally obstructing tumors [21].

4. Treatment response and survival prediction

The most direct prognostic application of pulmonary DWI is its use to predict, and subsequently to monitor, response to chemotherapy, radiotherapy, or chemoradiotherapy, since ADC changes during treatment often precede the volumetric tumor shrinkage that conventional RECIST-based CT assessment requires before response can be declared. Ohno and colleagues conducted a direct head-to-head comparison of DWI against FDG-PET/CT as predictors of treatment response

and overall survival in NSCLC patients receiving chemoradiotherapy, finding that pretreatment ADC and its early on-treatment change predicted both radiologic response and survival with accuracy at least comparable to metabolic PET parameters, a landmark result establishing DWI as a genuine prognostic, not merely diagnostic, tool [22]. Yabuuchi and colleagues, using combined dynamic contrast-enhanced and diffusion-weighted MRI, found that early post-treatment changes in ADC identified chemotherapy responders substantially earlier than anatomical tumor size criteria, a finding with direct implications for adapting ineffective regimens before patients accrue unnecessary toxicity [23]. Zhang and Kono similarly demonstrated in a monitoring study of solitary pulmonary nodules under chemotherapy that ADC rose in responding lesions ahead of measurable volumetric regression, corroborating the earlier-signal advantage of diffusion imaging over size-based response criteria [24].

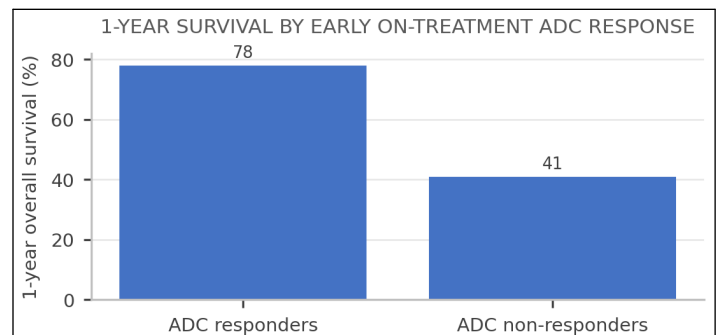


Figure 2: One-year overall survival in NSCLC patients receiving chemoradiotherapy, by early on-treatment ADC response versus non-response [22,23].

Luo and colleagues, studying patients with advanced NSCLC undergoing systemic therapy, confirmed that diffusion-weighted MRI response assessment tracked clinical outcome and could be incorporated into routine response evaluation protocols alongside CT, particularly for patients in whom repeated contrast-enhanced CT or PET/CT is undesirable due to renal function, contrast allergy, or cumulative radiation exposure [25]. Coolen and colleagues extended diffusion and dynamic

contrast-enhanced MRI to malignant pleural disease associated with thoracic malignancy, an important extension because pleural involvement independently worsens prognosis and is often incompletely characterized by CT alone [26].

5. Radiomic, histogram, and IVIM refinements

More recent work has moved beyond mean-ADC thresholds toward richer quantitative descriptors of the diffusion signal, seeking to extract additional prognostic information from the same acquisitions. Deng and colleagues applied whole-tumor histogram analysis of the ADC map, rather than a single region-of-interest mean value, and found that histogram parameters such as skewness and the lower percentiles of the ADC distribution improved discrimination between malignant and benign pulmonary lesions beyond what mean ADC alone achieved, an approach that better captures the intratumoral heterogeneity known to drive treatment resistance and poor prognosis [27]. Yuan and colleagues applied a broader radiomic framework, comparing a multiparametric radiomic biomarker with conventional volumetric analysis for decoding lung adenocarcinoma phenotypes associated with disease-free survival, and found that radiomic features, of which diffusion-derived texture is one component, outperformed volume alone in stratifying recurrence risk [28].

The IVIM framework, which separates the diffusion signal into a true diffusion coefficient and a perfusion-related pseudo-diffusion fraction by acquiring multiple b-values, has been applied specifically to lung cancer differentiation from obstructive consolidation. Wang and colleagues showed that IVIM-derived perfusion fraction correlated with pharmacokinetic parameters from dynamic contrast-enhanced MRI, indicating that the perfusion-sensitive component of the diffusion signal captures physiologically meaningful vascular information relevant to tumor biology [29]. Reproducibility remains a prerequisite for any of these refined metrics to enter

prognostic use; Wang and colleagues formally assessed the test-retest reproducibility of ADC measurement in lung cancer at 3T and reported coefficients of variation low enough to support ADC's use in longitudinal treatment-monitoring protocols [30].

Table 2: Quantitative diffusion metrics beyond mean ADC and their added prognostic value [27,28,29,30].		
Metric	Derivation	Added prognostic value
Histogram ADC percentiles/skewness	Whole-tumor ADC histogram	Captures heterogeneity beyond mean ADC [27]
Radiomic texture features	Multiparametric extraction	Outperforms volume for survival stratification [28]
IVIM perfusion fraction	Multi-b-value acquisition	Correlates with DCE-MRI vascular biology [29]
Test-retest reproducibility	Repeat 3T acquisition	Low CoV supports longitudinal monitoring [30]

6. Comparison with FDG-PET/CT and integration into clinical staging pathways

Because FDG-PET/CT remains the reference standard against which DWI is most often benchmarked, understanding where the two techniques converge and diverge is essential to positioning DWI's prognostic role. Peerlings and colleagues performed a systematic review and meta-analysis of MRI, including diffusion sequences, for determining pulmonary nodule malignancy, concluding that DWI-based protocols achieved diagnostic accuracy approaching that of PET/CT while avoiding radiation exposure, and identified nodal and metastatic staging as the domains with the strongest current evidence base for prognostically meaningful DWI use [31]. This convergence of accuracy, combined with DWI's absence of ionizing radiation, has made whole-body DWI protocols attractive particularly for younger patients, for repeated surveillance imaging, and for centers where PET/CT access is limited, a rationale directly supported by Ohno and colleagues' whole-body DWI M-staging comparison against integrated PET/CT [18].

Nonetheless, important limitations temper enthusiasm for DWI fully replacing PET/CT in prognostic staging. ADC values are influenced by technical factors including b-value selection, echo time, respiratory motion compensation strategy, and magnet field strength, all of which vary across the published literature and complicate direct threshold comparison between centers, a concern already flagged in the earliest consensus recommendations for oncologic DWI [3]. Benign entities with high cellularity, active inflammation, or abscess formation can mimic the low-ADC signature of malignancy, producing false positives that parallel, though do not fully replicate, the false-positive pattern seen with FDG-PET/CT in granulomatous disease, meaning DWI does not eliminate but rather shifts the sources of diagnostic and prognostic ambiguity [7,11]. The overall weight of evidence nonetheless supports a layered approach in which DWI, interpreted alongside conventional CT morphology and used selectively alongside or in place of PET/CT depending on clinical context, contributes meaningful, radiation-free prognostic information across the diagnostic, staging, and treatment-response phases of pulmonary nodule and lung cancer management.

7. Conclusion

Two decades of accumulating evidence support diffusion-weighted imaging, and its principal quantitative output the apparent diffusion coefficient, as a genuine prognostic tool in the evaluation of pulmonary nodules, extending well beyond its original role as a malignancy-characterization test [5,4]. ADC values correlate with tumor cellularity and histologic subtype at the tissue level, carry independent prognostic weight for nodal and distant staging comparable to FDG-PET/CT in several head-to-head series, and change early during treatment in a pattern that anticipates eventual radiologic response and overall survival more rapidly than size-based CT criteria alone [9,17,22]. Histogram, radiomic, and IVIM-based refinements of the basic ADC

metric are extracting additional prognostic signal from the same underlying acquisitions, though standardization of acquisition parameters and further reproducibility validation remain necessary before these richer descriptors are ready for routine prognostic use [27,30]. Taken together, the literature supports incorporating DWI, alongside rather than strictly in place of conventional CT and PET/CT, into the prognostic evaluation of pulmonary nodules, with the technique's radiation-free acquisition making it particularly well suited to the repeated imaging that prognostic surveillance and treatment-response monitoring require [31,3].

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