

Diagnostic Pitfalls of 18 F-FDG PET/CT in Presumed Malignant Pulmonary Nodules and Masses: A Retrospective Pathology-Based Study

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Research Article

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Abstract

Objective

To characterize CT morphological and metabolic features of pulmonary nodules and masses initially considered suspicious for malignancy on ^{18}F -FDG PET/CT and to explore features associated with benign false-positive interpretations.

Methods

We retrospectively analyzed 31 patients with pulmonary nodules or masses considered suspicious for malignancy on ^{18}F -FDG PET/CT who subsequently underwent definitive pathological evaluation. Patients were categorized into malignant ($n = 21$) and benign false-positive ($n = 10$) groups. Firth penalized logistic regression was used to assess associations between CT morphological features, clinical characteristics, and false-positive outcomes.

Results

No significant difference in SUVmax was observed between the two groups. The prevalence of spiculation (80.0% vs. 33.3%, $p = 0.023$) and pleural indentation (60.0% vs. 14.3%, $p = 0.015$) was significantly higher in the benign false-positive group than in the malignant group. In multivariable Firth regression, spiculation was independently associated with false-positive outcomes (adjusted OR, 11.80; 95% CI, 1.97–106.87; $p = 0.005$), whereas serum tumor marker positivity was associated with lower odds of false-positive interpretation (adjusted OR, 0.09; 95% CI, 0.01–0.63; $p = 0.013$). Granulomatous inflammatory lesions and fungal infections accounted for 80% of benign false-positive lesions.

Conclusion

In pulmonary lesions presumed malignant on ^{18}F -FDG PET/CT, benign inflammatory and infectious diseases may reproduce both increased FDG uptake and malignant-like CT morphology. Spiculation and pleural indentation should therefore be interpreted cautiously, particularly when serum tumor markers are negative. Integration of clinical, imaging, pathological, and multidisciplinary information may help reduce unnecessary invasive management.

1. Introduction

^{18}F -FDG PET/CT is routinely utilized for the non-invasive differentiation of pulmonary nodules and masses(1, 2). However, because ^{18}F -FDG is not a tumor-specific tracer, intense inflammatory cell

infiltration induced by active granulomatous or fungal infections can exhibit marked hypermetabolism, leading to false-positive misdiagnoses(3–5).

In clinical practice, radiologists routinely interpret PET/CT findings in conjunction with co-registered CT morphological features, such as spiculation and pleural indentation(6). Classical radiological paradigms regard spiculation as a cardinal indicator of malignancy(7). Nevertheless, within specific patient cohorts pre-selected as "suspected malignant" by PET/CT—which encompass both hypermetabolic lesions and low-metabolism lesions selected due to highly suspicious morphology—the diagnostic utility of these morphological signs warrants re-evaluation. Because this cohort inherently filters out conventional benign lesions displaying both low metabolism and benign morphology, the remaining benign lesions predominantly consist of severe inflammatory processes accompanied by marked fibroproliferation and tissue remodeling, thereby altering the expected distribution of classic malignant signs(8, 9).

This study retrospectively analyzes a cohort of pulmonary nodules/masses suspected of malignancy on PET/CT to characterize the relationship between CT morphological signs and false-positive outcomes, aiming to provide evidence for reducing clinical misdiagnoses(10, 11).

2. Materials and Methods

2.1 Patient Selection

Clinical and imaging data of 31 patients with pulmonary nodules/masses initially suspected of malignancy on ^{18}F -FDG PET/CT and confirmed by definitive histopathology were retrospectively reviewed. Patients were categorized based on final pathological diagnoses into a true-positive group (primary lung carcinoma, $n = 21$) and a false-positive group (non-neoplastic benign lesions, $n = 10$) (12).

2.2 Imaging and Clinical Parameters

Patient age, sex, smoking history, serum tumor marker status (CEA, SCC, NSE, ProGRP, CYFRA21-1, CA125, CA72-4), maximum lesion diameter, SUVmax, and CT morphological features (spiculation, lobulation, pleural indentation) were documented.

2.3 Statistical Analysis

Continuous variables are expressed as median and interquartile range (IQR) and compared using the Wilcoxon rank-sum test. Categorical variables are presented as counts and percentages and evaluated using Fisher's exact test.

Given the sample size ($N = 31$) and event count ($n = 10$ false-positive outcomes), standard logistic regression is susceptible to estimation bias and parameter instability(13). Therefore, Firth penalized logistic regression (logistf package in R) was employed to evaluate factors associated with false-positive outcomes, calculating profile likelihood confidence intervals(14). Given the small number of

false-positive events, the multivariable model was restricted to two prespecified variables to limit model complexity and reduce the risk of overfitting. Two-sided $p < 0.05$ was considered statistically significant.

3. Results

3.1 Baseline Clinical and Imaging Characteristics

SUVmax showed no statistically significant difference between the two groups (false-positive: 8.9 vs. malignant: 7.4, $p = 0.410$)(Figure 1). The cohort included 5 cases with $SUV_{max} \leq 2.5$, all initially categorized as suspected malignant on PET/CT due to suspicious CT morphological features. The prevalence of spiculation (80.0% vs. 33.3%, $p = 0.023$) and pleural indentation (60.0% vs. 14.3%, $p = 0.015$) was significantly higher in the false-positive benign group than in the malignant group (Table 1, Figure 2).

Pathological evaluation revealed that adenocarcinoma (61.9%) and squamous cell carcinoma (28.6%) predominated in the true-positive group, whereas granulomatous inflammation/tuberculosis (50.0%) and fungal infections (20.0%) comprised the majority of the false-positive group (Table 2).

Table 1. Baseline Clinical and Imaging Characteristics of the Study Population.

Variable	Total (N=31)	Malignant (TP, n=21)	Benign (FP, n=10)	p-value
Age (years)	65.0 (59.5–68.0)	66.0 (61.0–69.0)	58.5 (53.2–65.5)	0.049*
Sex (Male)	18 (58.1%)	11 (52.4%)	7 (70.0%)	0.449
Smoking history (Ever)	10 (32.3%)	7 (33.3%)	3 (30.0%)	>0.999
SUVmax	7.8 (5.0–13.1)	7.4 (4.5–12.9)	8.9 (6.7–16.2)	0.398
Lesion size (cm)	2.5 (1.7–3.4)	2.5 (1.7–3.6)	2.5 (1.6–3.0)	0.812
Spiculation	15 (48.4%)	7 (33.3%)	8 (80.0%)	0.023*
Pleural indentation	9 (29.0%)	3 (14.3%)	6 (60.0%)	0.015*
Lobulation	13 (41.9%)	7 (33.3%)	6 (60.0%)	0.246
Tumor markers (Positive) ^a	11 (35.5%)	10 (47.6%)	1 (10.0%)	0.055

Data are presented as median (interquartile range) or number (percentage).

*Statistically significant ($p < 0.05$).

a Positive for any of the tested serum markers (CEA, SCC, NSE, ProGRP, CYFRA21-1, CA125, CA72-4).

Abbreviations: FP, false-positive; IQR, interquartile range; SUVmax, maximum standardized uptake value; TP, true-positive.

3.2 Histopathological Distribution

Table 2. Histopathological Breakdown of Malignant and Benign Lesions.

Histological Classification	Cases (n)	Percentage (%)
Malignant Group (n = 21)		
Adenocarcinoma	13	61.9%
Squamous cell carcinoma	6	28.6%
Sarcomatoid carcinoma	1	4.8%
Spindle cell neoplasm	1	4.8%
Benign Group (False-Positive, n = 10)		
Granulomatous inflammation/ Tuberculosis	5	50.0%
Pulmonary fungal infections (Cryptococcosis, Aspergillosis)	2	20.0%
Organizing pneumonia and lung abscess	1	10.0%
Reactive pneumonitis, epithelial metaplasia, and fibrosis	2	20.0%

Data are presented as absolute numbers and percentages (n%).

Percentages may not sum to 100% due to rounding. All benign lesions represented false-positive findings on ¹⁸F-FDG PET/CT.

3.3 Firth Penalized Logistic Regression Analysis

Univariable analysis revealed that age < 60 years, spiculation, and pleural indentation were positively associated with false-positive outcomes, whereas positive serum tumor markers showed a negative association (Table 3).

Following multivariable Firth regression adjustment, spiculation remained independently associated with false-positive outcomes (Adjusted OR = 11.80, 95%CI: 1.97 - 106.87, p = 0.005), while tumor marker positivity functioned as a protective factor (Adjusted OR = 0.09, 95%CI: 0.01 - 0.63, p = 0.013) (Table 3).

Table 3. Firth Penalized Logistic Regression Analysis of Factors Associated With Benign False-Positive Outcomes

Variable	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI) ^a	p-value
Age < 60 years	5.29 (1.06–30.38)	0.042*	—	—
Spiculation (Present)	6.57 (1.38–42.30)	0.017*	11.80 (1.97–106.87)	0.005*
Pleural indentation (Present)	7.63 (1.55–45.38)	0.012*	—	—
Tumor markers (Positive)	0.17 (0.02–0.96)	0.044*	0.09 (0.01–0.63)	0.013*

Statistically significant (p < 0.05).

^a Multivariable model adjusted for spiculation and tumor marker status, conforming to the events-per-variable constraint (n = 10).

Abbreviations: CI, profile likelihood confidence interval; OR, odds ratio.

4. DISCUSSION

This study demonstrates that among pulmonary nodules/masses initially suspected of malignancy on PET/CT, the prevalence of spiculation in the false-positive benign group is significantly higher than in the malignant group, maintaining an independent association with false-positive outcomes in multivariable analysis.

This discrepancy with classical radiological concepts may partly reflect the selected nature of the study population. In unselected or general patient populations, spiculation is predominantly observed in malignant neoplasms. However, within a cohort pre-filtered by PET/CT as "suspected malignant," typical benign lesions lacking metabolic abnormalities and displaying smooth morphology have already been excluded(15, 16). Consequently, the benign lesions remaining in the false-positive group consist chiefly of active granulomas or fungal infections (Figure 3)(17, 18).

Histopathological findings support this mechanism (Table 2, Figure 3, Supplementary Table 1). Granulomatous inflammatory lesions and fungal infections accounted for 80% of benign false-positive lesions. During active phases of these infections, local inflammatory infiltration drives elevated metabolic activity(8, 9). These inflammatory and infectious lesions may produce fibrotic and architectural changes that manifest as spiculation and pleural indentation on CT, potentially mimicking malignant morphology(19-21).

For clinical decision-making, these findings suggest that inflammatory or infectious mimics should remain in the differential diagnosis when lesions presumed malignant on PET/CT show spiculation, particularly in the setting of negative serum tumor markers. Depending on the clinical context,

multidisciplinary review, targeted infectious evaluation, or percutaneous biopsy may help clarify the diagnosis before definitive treatment(22, 23). Such "high-risk false-positive" cases should undergo multidisciplinary team (MDT) review, targeted fungal/tuberculosis serological screening, or percutaneous biopsy to prevent unnecessary surgical resections (24, 25). Based on the findings of this study, we propose a practical diagnostic framework for pulmonary lesions presumed malignant on ^{18}F -FDG PET/CT (Figure 4).

4.1 Limitations

Several limitations of this study should be acknowledged:

First, this was a single-center retrospective study with a modest sample size ($N = 31$, $n = 10$ false positives). Although Firth penalized regression was applied to minimize parameter estimation bias inherent to small samples(26), confidence intervals remained relatively wide; thus, findings require validation in larger, prospective multicenter cohorts.

Second, all enrolled patients underwent surgical resection or core needle biopsy to achieve definitive pathological diagnosis. This entry criterion introduces potential selection bias by excluding low-risk lesions managed conservatively with imaging follow-up.

Third, visual assessment of CT morphological features involves inherent inter-observer variability. Future studies integrating quantitative radiomics or deep learning algorithms may provide more objective, automated morphological phenotyping.

5. Conclusion

In patients with pulmonary lesions presumed malignant on ^{18}F -FDG PET/CT, benign inflammatory and infectious diseases may reproduce both increased FDG uptake and malignant-like CT morphology. In this pathology-confirmed cohort, spiculation was strongly associated with benign false-positive interpretation, whereas SUVmax alone did not distinguish benign from malignant lesions. These findings suggest that spiculation and pleural indentation should be interpreted cautiously in the appropriate clinical context, particularly when serum tumor markers are negative. Larger multicenter studies are needed to validate these observations.

Abbreviations

Abbreviation	Full term
¹⁸ F-FDG	18F-fluorodeoxyglucose
PET/CT	Positron emission tomography/computed tomography
CT	Computed tomography
SUVmax	Maximum standardized uptake value
FP	False positive
TP	True positive
MDT	Multidisciplinary team
OR	Odds ratio
CI	Confidence interval
IQR	Interquartile range
TB	Tuberculosis

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of The First Affiliated Hospital of Zhengzhou University. Owing to the retrospective nature of this study, the requirement for written informed consent was waived by the committee. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Data use agreements were signed among participating institutions.

Clinical trial number

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to privacy/ethical restrictions on patient medical record data but are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

Penghao Zhao and Chunyang Zhang collected the data. Penghao Zhao designed the study. Penghao Zhao analyzed the data. Penghao Zhao and Chunyang Zhang interpreted the data. Penghao Zhao prepared the manuscript, and Chunyang Zhang revised it critically. All authors read and approved the final manuscript.

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Not applicable.

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Figures

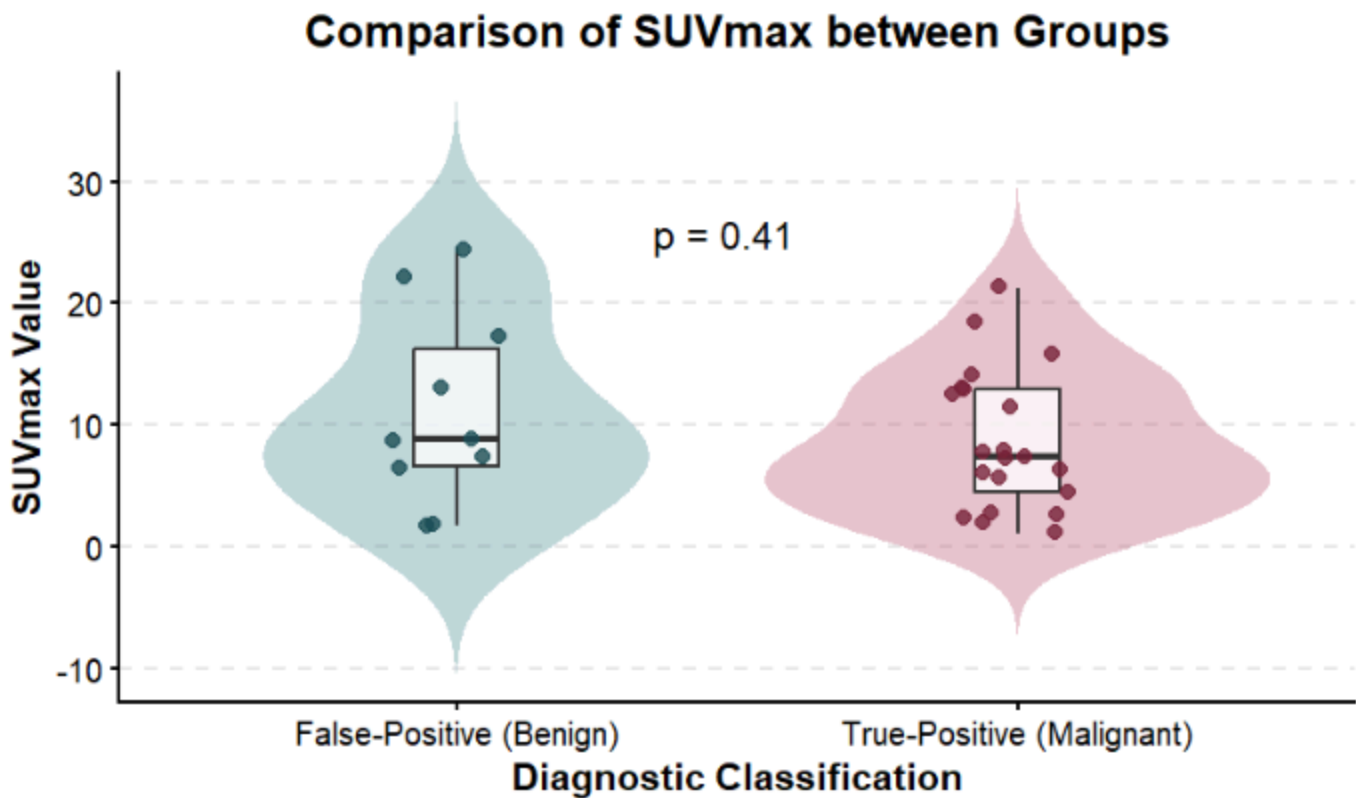


Figure 1

Comparison of lesion metabolic parameters (SUVmax) across diagnostic groups.

Violin plots with overlaid boxplots show no statistically significant difference in SUV_{max} between the two groups ($p = 0.41$). Points represent individual lesions.

Comparison of Significant Morphological Features

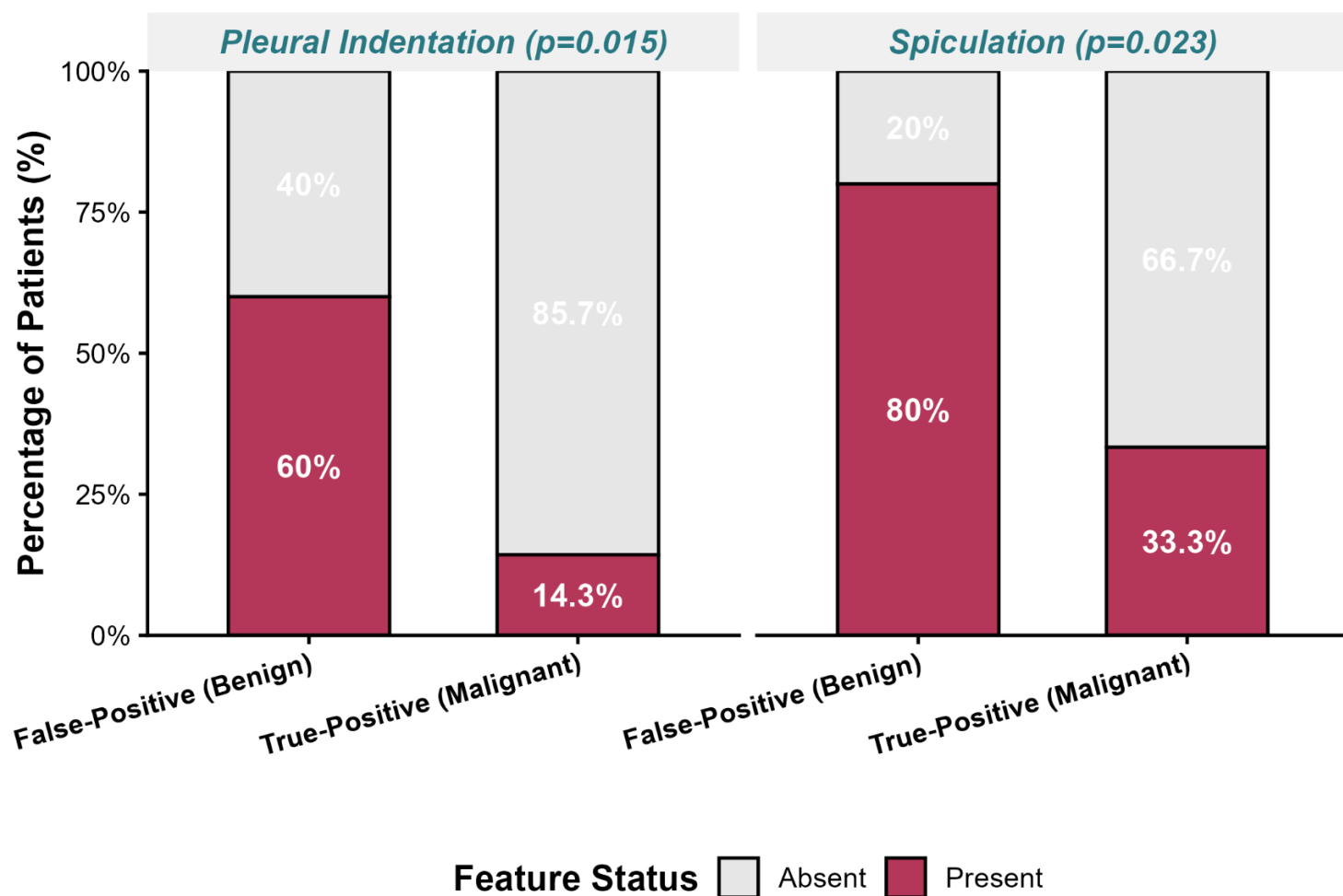


Figure 2

Paradoxical distribution patterns of core HRCT morphological signs.

Stacked bar charts comparing the prevalence of pleural indentation ($p = 0.015$) and spiculation ($p = 0.023$) between false-positive (benign) and true-positive (malignant) cohorts.

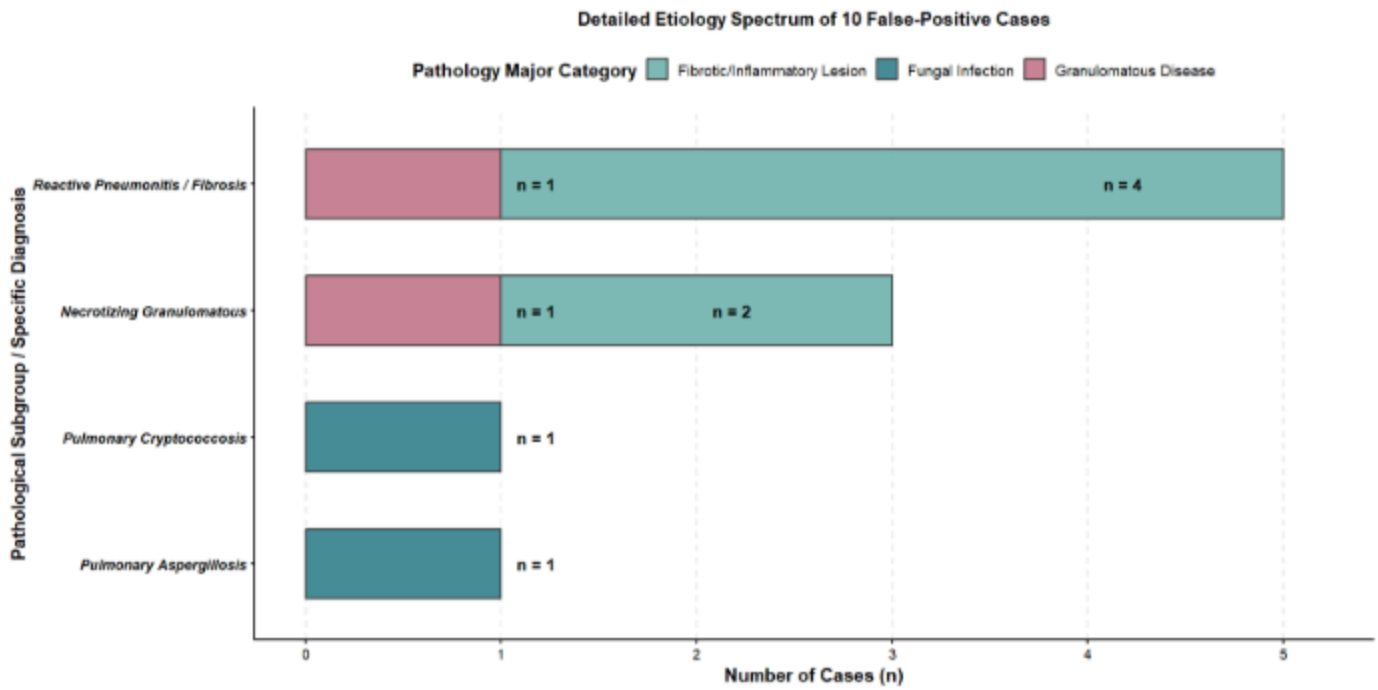


Figure 3

Detailed histopathological etiology spectrum of 10 false-positive cases.

Distribution of specific pathological diagnoses (n = 10) categorized by major pathological entities.

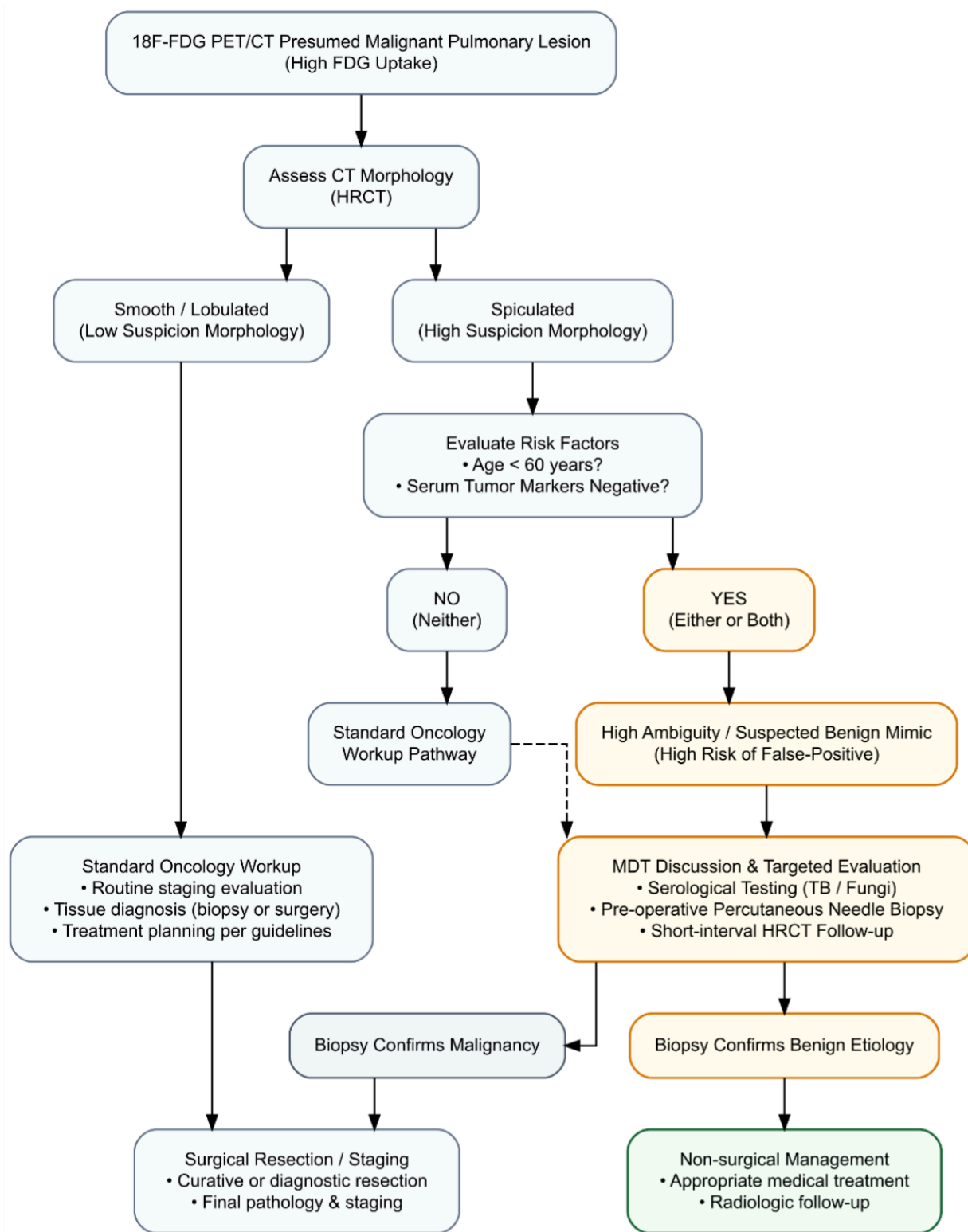


Figure 4

Proposed diagnostic considerations for pulmonary lesions presumed malignant on ^{18}F -FDG PET/CT.

A structured diagnostic workflow incorporating high-resolution CT (HRCT) morphology and clinical risk factor evaluation to identify benign mimics, guide targeted multidisciplinary evaluation, and prevent unnecessary surgical resection.

