A comparative review of the application value of FAPI PET/CT and ^{18}F-FDG PET/CT in lung cancer

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Abstract
Fibroblast activation protein inhibitor (FAPI) positron emission tomography/computed tomography (PET/CT) is a multimodal imaging technique that combines PET and CT, utilizing FAP inhibitors as radiotracers. Fibroblast activation protein, a serine protease highly expressed in many epithelial tumor-associated fibroblasts, plays a crucial role in tumor stroma formation and remodeling. Through the detection of FAP expression, FAPI PET/CT facilitates the diagnosis and staging of both benign and malignant pulmonary tumors. In contrast to traditional fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT focusing on glucose metabolism, FAPI PET/CT offers benefits such as enhanced specificity, reduced background noise, accelerated imaging speed, and decreased radiation exposure. This review provides an overview of the progress in applying FAPI PET/CT and ^{18}F-FDG PET/CT in pulmonary malignancies and discusses current challenges and future prospects.

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Introduction

Lung cancer is the leading cause of cancer-related deaths [1, 2]. Data indicates that nearly 350 individuals die from lung cancer daily, surpassing the mortality rate of the second most fatal cancer, colorectal cancer, by almost 2.5 times [1]. In 2023, out of 127,070 documented lung cancer deaths, an estimated 103,000 cases were associated with direct smoking, while 3,560 cases were connected to secondhand smoke exposure [1]. Since lung cancer has not obvious symptoms in the early stage, most patients are already in the advanced stage at the time of diagnosis, resulting in poor therapeutic outcomes and poor prognosis [3]. Therefore, early detection, accurate diagnosis, precise staging and effective treatment are crucial to improve the survival rate and quality of life of lung cancer patients [4].

Positron emission tomography/computed tomography (PET/CT) is widely utilized in nuclear medicine for the diagnosis, staging, treatment assessment, and surveillance of lung cancer [5, 6]. It uses radioactive nuclide-labeled biomolecules as imaging agents to show the functional or metabolic status of tissues or organs at the molecular level, along with CT to provide anatomical details [7]. The most commonly used PET imaging tracer is fluorine-18-fluorodeoxyglucose (^{18}F-FDG), a glucose analogue that can be taken up and accumulated by tumor cells due to their increased glucose metabolic activity, revealing high metabolic activity on PET images [7]. Additionally, several factors are crucial in ^{18}F-FDG PET/CT imaging [8, 9]: (1) ^{18}F-FDG uptake not only by tumor cells but also by normal tissues or non-neoplastic lesions may result in false-positive results; (2) low ^{18}F-FDG uptake in certain poorly differentiated or hypoxic tumor cells can lead to false-negative findings; (3) ^{18}F-FDG shows high background signals in essential metabolically active organs like the brain, heart, liver, and kidneys, affecting tumor detection in these regions; and (4) preparation for ^{18}F-FDG PET/CT requires patient fasting and regulation of blood glucose levels before the scan to reduce ^{18}F-FDG distribution and uptake in healthy tissues. Hence, the quest for more effective, safer, and targeted PET tumor imaging agents stands as a crucial trajectory in the advancement of PET/CT technology.

In recent years, significant attention and research effort have been devoted to a novel PET imaging agent-fibroblast activator protein inhibitor (FAPI) [10]. Fibroblast activator protein inhibitor, a category of small-molecule enzyme activity inhibitors, exhibit specific

binding to FAP and are radiolabeled with isotopes [e.g., ^{18}F, gallium-68 (^{68}Ga)] for PET imaging [10]. Fibroblast activator protein, a serine protease from the dipeptidyl peptidase family, functions by degrading proteins in the surrounding tissues, thereby facilitating protein breakdown and matrix restructuring [11]. Widely prevalent in epithelial tumor-associated fibroblasts linked to liver, colorectal, pancreatic, and ovarian cancers, FAP plays a pivotal role in tumor stroma formation, maintenance, as well as influencing tumor cell behaviors such as proliferation, invasion, metastasis, and evasion from the immune system [12-14]. In contrast to ^{18}F-FDG, FAP exhibits minimal to negligible expression in normal tissues, benign tumor stroma, and non-neoplastic lesions [10]. Consequently, the implementation of FAPI PET/CT capitalizes on FAP as a distinct marker for tumor stroma, thereby enhancing tumor detection and differentiation [10, 11].

To thoroughly evaluate the clinical application value of FAPI PET/CT and ^{18}F-FDG-PET/CT in diagnosing primary and metastatic lesions of lung cancer, as well as to explore the latest research progress of these two techniques, we conducted a comprehensive review study. In this endeavor, we performed a detailed literature review encompassing relevant studies published up to January 31, 2024, utilizing databases such as PubMed, EMBASE, and Web of Science with the keywords "FAPI-PET", "FDG-PET", and "lung cancer". Through this review, we aim to provide a detailed comparison and analysis of the relative advantages and limitations of FAPI PET/CT and ^{18}F-FDG-PET/CT in lung cancer diagnosis, focusing on key metrics like diagnostic accuracy, sensitivity, specificity, false-positive rate, and false-negative rate. The ultimate goal is to offer scientifically sound and reasonable guidance to clinicians in selecting appropriate diagnostic tools and to direct future research in this crucial field.

Application of FAPI PET/CT in lung cancer

Diagnostic value of FAPI-PET/CT in primary lung cancer

Limited published studies have explored the clinical utility of FAPI PET/CT in diagnosing lung cancer. Wei et al. (2023) [15] conducted a study involving 68 lung cancer patients, revealing that compared to ^{18}F-FDG PET/CT, ^{18}F-FAPI PET/CT exhibited higher sensitivity (99% vs. 87%), specificity (93% vs. 79%), accuracy (97% vs. 85%), and negative predictive value (97% vs. 70%). Nevertheless, the positive predictive value between the two imaging modalities was similar (98% vs. 92%). In another study, Li et al. (2021) [16] evaluated the efficacy of ^{18}F-FAPI-42 PET/CT and ^{18}F-FDG PET/CT in newly diagnosed lung cancer patients, finding comparable detection rates of primary lung lesions (both 100%), corroborating the conclusions drawn by Wu et al. (2022) [17]. In normal lung tissue, the uptake of ^{68}Ga-FAPI was substantially low, comparable to that of ^{18}F-FDG [standardized uptake value maximum (SUVmax) 0.48 vs. 0.46, P=0.056] [18]. Furthermore, in 8 patients with lung metastases, no significant variance in uptake was observed between ^{68}Ga-FAPI and ^{18}F-FDG (SUVmax 6.68 vs. 11.48, P=0.641). Given the analogous uptake in normal lung tissue, this suggests a similarity in the tumor-to-background ratio (TBR) of lung lesions between FAPI PET/CT and ^{18}F-FDG PET/CT [18], highlighting the comparable capabilities of FAPI PET/CT and ^{18}F-FDG PET/CT in detecting lung lesions.

Epithelial tumors, including lung adenocarcinoma and squamous cell carcinoma, demonstrated similar uptake capacities for both tracers (12.24±3.97 vs. 12.04±5.75). In contrast, non-epithelial tumors, such as small cell lung cancer and high-grade neuroendocrine tumors, exhibited significantly lower uptake of ^{18}F-FAPI-42 compared to ^{18}F-FDG (8.05±2.60 vs. 16.28±5.17) [16]. This suggests that ^{18}F-FAPI-42 PET/CT may be more appropriate for diagnosing epithelial lung cancer, while alternative imaging modalities may be necessary for non-epithelial lung cancers. Some studies indicate differences in the uptake values of ^{18}F-FAPI-04 between primary and metastatic lesions in lung cancer patients with similar pathology types, with the former notably higher [19]. Wu et al. (2022) [17] revealed no significant disparities in SUVmax or TBR values between the two tracers. However, Wang et al. (2022) [20] concluded that ^{68}Ga-FAPI PET/CT, compared to ^{18}F-FDG PET/CT, yielded significantly higher SUVmax (13.7 vs. 10.4, P=0.02) and TBR values (34.2 vs. 25.9, P=0.02), suggesting its suitability for early lung cancer detection. This difference may be attributed to the study population primarily comprising patients with large tumors (average size: 3.3cm) and advanced disease, in contrast to Wu et al.'s (2022) study [17] involving tumors of varying sizes and stages. These results highlight how the efficacy of FAPI PET/CT in lung cancer diagnosis is influenced by tumor pathology, size, and staging. Consequently, FAPI PET/CT is not a substitute for ^{18}F-FDG PET/CT, and the selection of appropriate tracers and methods should align with specific clinical contexts and objectives to improve the precision and sensitivity of lung cancer diagnosis.

Recent studies have extended the application of FAPI PET/CT beyond lung cancer diagnosis to examine its imaging impact in fibrotic interstitial lung disease. Röhrich et al. (2022) [21] utilized ^{68}Ga-FAPI-46 PET/CT imaging to assess patients with fibrotic interstitial lung disease and lung cancer, demonstrating the effectiveness of this technique for both conditions. A multidisciplinary team conducted a differential diagnosis between fibrotic interstitial lung disease and lung cancer based on clinical findings, radiological features on CT scans, and lung biopsies from 8 out of 15 patients. The study revealed similar FAPI-46 uptake levels in fibrotic and neoplastic lesions; however, the SUVmax and SUVmean decreased more rapidly in fibrotic lesions and background tissues over time compared to neoplastic lesions. Consequently, there was a higher TBR in neoplastic lesions at 10, 60, and 180 minutes post-injection. These findings suggest that FAPI PET/CT imaging can effectively differentiate between fibrotic interstitial lung disease and lung cancer by observing distinct trends in TBR changes during dynamic imaging. This approach serves as a valuable tool for patients with overlapping symptoms or challenging differential diagnoses.

Diagnostic value of FAPI PET/CT for lymph node metastasis in lung cancer

Lymph node staging plays a crucial role in the comprehensive staging of lung cancer, offering insights into tumor aggressiveness and metastatic potential, thereby influencing treatment decisions and prognosis assessment [22]. Currently, ^{18}F-FDG PET/CT stands as the primary imaging modality for lung cancer staging, demonstrating notable sensitivity and specificity, particularly in evaluating lymph nodes [23].

In a prospective study [17], ^{68}Ga-FAPI proved superior to ^{18}F-FDG PET/CT [9/15 (60.0%) vs. 5/15 (33.3%)] in patient-based analysis (93.0% vs. 86.0%). Among the 10 patients who underwent mediastinal lymph node dissection in this study, 180 nodes were biopsied, revealing 11 as malignant and 169 as benign. The diagnostic performance of ^{68}Ga-FAPI and ^{18}F-FDG PET/CT in identifying malignant nodes was 81.8% (9/11) and 97.6% (165/169), and false positives were 72.7% (8/11) and 88.8% (150/169), respectively. It is noteworthy that ^{68}Ga-FAPI PET/CT resulted in N stage downstaging for one patient due to missed metastasis, yet led to N stage upstaging for another patient by detecting additional false-positive nodes. In contrast, ^{18}F-FDG PET/CT revealed false-positive nodes in five patients, resulting in upstaging of their N stage. Overall, the N-stage accuracy for non-small cell lung cancer patients based on ^{68}Ga-FAPI PET/CT findings was superior (80% [8/10] vs. 50% [5/10]) compared to ^{18}F-FDG PET/CT, albeit without statistical significance (P=0.16). These findings highlight that ^{68}Ga-FAPI and ^{18}F-FDG radiotracers exhibit distinct strengths and weaknesses in detecting mediastinal lymph node metastasis through PET/CT imaging, impacting N stage outcomes variably. Notably, ^{68}Ga-FAPI excels in reflecting the expression of FAP in mediastinal lymph nodes, while ^{18}F-FDG is proficient at reflecting the metabolic activity of tumor cells within these nodes.

In a study by Li et al. (2021) [16] involving 28 patients with lung adenocarcinoma and squamous carcinoma suspected of harboring lymph node metastases, ^{18}F-FAPI-42 PET/CT surpassed ^{18}F-FDG PET/CT by detecting more lymph node lesions with higher SUVmax values. This superiority is attributed to the higher expression levels of FAP in the tumor microenvironment of epithelial tumors like lung adenocarcinoma and squamous carcinoma [19]. Besides, ^{18}F-FAPI-42 PET/CT outperformed ^{18}F-FDG PET/CT in detecting positive lymph node lesions aiding clinicians in precise treatment planning. However, the study observed that in cases of small cell lung cancer and high-grade neuroendocrine tumors, ^{18}F-FAPI-42 PET/CT lagged behind ^{18}F-FDG PET/CT in diagnosing lymph node metastasis, as it identified fewer lesions with lower SUVmax values. This discrepancy can be attributed to the lower FAP expression levels in the tumor microenvironment of non-epithelial tumors like small cell lung cancer, whereas ^{18}F-FDG is broadly effective in reflecting tumor metabolic activities [19]. From the FAPI PET/CT study by Wei et al. (2022) [19] the SUVmax levels indicated that lung squamous cell carcinoma surpassed lung adenocarcinoma and small cell carcinoma (P<0.001), with lung adenocarcinoma outscoring small cell carcinoma (P=0.0256) in primary tumor assessments. These findings signal varying impacts and insights of FAPI PET/CT in different lung cancer types, offering superior delineation in epithelial tumors (e.g., lung squamous cell and adenocarcinomas) compared to non-epithelial tumors like small cell lung cancer. These results bear significance for clinical practice as they aid physicians in choosing optimal imaging agents and methods to enhance the diagnostic efficacy of lymph node metastasis assessment, also shedding light on exploring the molecular heterogeneity and biological characteristics of different lung cancer types.

Diagnostic value of FAPI PET/CT for distant metastasis of lung cancer

The prognosis of distant metastasis in lung cancer is multifaceted, influenced by factors including metastatic site, number, extent, and velocity, alongside patient age, comorbidities, treatment efficacy, among others [24]. A population-based study revealed that lung metastases with distant dissemination had a median survival of approximately 6 months [24], emphasizing the critical role of enhancing the diagnostic accuracy of distant metastasis in lung cancer for informed treatment decisions and improved quality of life [25, 26].

Fibroblast activation protein inhibitor is highly expressed in tumor stroma but almost absent in normal or inflamed tissues, effectively reducing false positive results [11]. In FAPI PET/CT imaging, the uptake in normal tissues like the brain, myocardium, and spleen is minimal, facilitating the detection of small tumor foci. Fibroblast activation protein inhibitor uptake is markedly reduced in certain inflammatory conditions such as infections, tuberculosis, and autoimmune diseases, aiding in the differentiation from malignant metastatic lymph nodes [11, 16]. On the contrary, FAPI exhibits a high sensitivity towards certain low-metabolism or low-differentiation tumors, consequently enabling a reduction in false-negative outcomes. For instance, in tumors with restrained metabolism or limited differentiation such as bronchial carcinoid, pleural mesothelioma, and neuroendocrine tumors, the uptake of FAPI typically surpasses that of normal tissue or significantly exceeds that of ^{18}F-FDG. This distinction allows for the precise diagnosis of these tumors and identification of distant metasta-ses [16]. Furthermore, FAPI exclusively portrays the activity level of the tumor stroma and remains unaffected by factors like size, number, location, density, or morphology of metastases. As a result, it can effectively detect and pinpoint small metastatic lesions or cystic and necrotizing metastatic lesions within the thoracic or abdominal cavity [11, 16].

It is widely acknowledged that ^{18}F-FDG PET/CT has limitations in detecting brain metastases due to the high background radioactivity in the brain [27]. In contrast, ^{68}Ga-FAPI does not accumulate in brain tissue, which presents a potential solution to this issue [28]. Several case reports [29, 30] have indicated that ^{68}Ga-FAPI PET/CT shows higher sensitivity in detecting brain metastases. A study [20] revealed that the TBR of ^{68}Ga-FAPI PET/CT was significantly higher than ^{18}F-FDG PET/CT (TBR-FAPI to TBR-^{18}F-FDG ratio: 333.7) and detected more brain metastases (23 vs. 10). However, the effectiveness of ^{68}Ga-FAPI PET/CT was still inferior to that of MRI. The uptake of ^{68}Ga-FAPI in brain metastases varied considerably, with almost half of the lesions (11 out of 23) showing low tracer uptake (SUVmax 2.5), which may also be a limitation of ^{68}Ga-FAPI PET/CT [20].

Fluorine-18-FDG PET/CT has proven to be an effective tech-

nique in detecting bone metastases [31], exhibiting high sensitivity comparable to bone scanning but with greater specificity [32, 33]. In contrast, ^{68}Ga-FAPI PET/CT identified a higher number of suspected bone metastatic lesions than ^{18}F-FDG PET/CT (109 vs. 91), particularly in detecting small bone lesions [20]. Similar conclusions have been drawn in other studies [17, 34, 35], with findings indicating the superior sensitivity of ^{68}Ga-FAPI PET/CT over ^{18}F-FDG PET/CT. These findings have important implications for early detection of bone metastases and developing corresponding treatment options.

Gallium-68-FAPI PET/CT offers distinctive benefits that extend beyond the detection of bone metastases, especially in identifying visceral metastases. A prime example of its superiority is its enhanced capability to detect suspected pleural metastatic lesions in comparison to ^{18}F-FDG PET/CT [20]. This proficiency is crucial for diagnosing the causes of pleural effusion and guiding clinical decisions. The study of Wang et al. (2022) [20] showed that ^{68}Ga-FAPI PET/CT was identical to ^{18}F-FDG PET/CT in diagnose metastasis of distant organs such as lung, liver and adrenal glands. Remarkably, the work of Wu et al. (2022) [17] indicates that while FAPI-PET/CT surpasses ^{18}F-FDG PET/CT in diagnosing liver metastases with a striking accuracy rate (100% vs. 25%), it may exhibit reduced effectiveness in other areas. This discrepancy could be due to the small sample size, underscoring the importance of considering diagnostic accuracy when selecting the appropriate imaging modality.

Limitations

Despite the valuable insights provided by the analyzed studies, it is important to note several limitations that could potentially impact the reliability and generalizability of the results. Firstly, the small sample sizes in some of the studies may limit the statistical power and ability to detect significant differences. Secondly, the inconsistent lymph node biopsy methods used across studies may introduce variability in the assessment of disease status and response to treatment. Finally, the variable radiotracer doses administered during PET/CT scans may affect image quality and detection rates, further compromising the accuracy of the results. To address these limitations and elevate the quality and validity of future studies, researchers should consider increasing sample sizes to achieve greater statistical power, standardizing biopsy methods to reduce variability, and controlling radiotracer doses to ensure optimal image quality.

In conclusion, FAPI PET/CT, as a multimodal imaging technique, has demonstrated significant clinical value in the early detection and accurate staging of lung cancer. Compared to traditional ^{18}F-FDG PET/CT, FAPI PET/CT provides novel insights and enhanced precision in identifying malignant tumors, as well as distinguishing benign from malignant lung nodules. However, to fully realize its potential, we must address several crucial technical challenges, such as improving imaging resolution and reducing costs. Future research should prioritize optimizing the imaging parameters of FAPI PET/CT, developing novel tracers to enhance tumor-specific identification, and exploring its applicability in diverse tumor types. Furthermore, researchers should consider how to seamlessly integrate FAPI PET/CT into current clinical workflows to achieve more precise diagnosis and tailored treatment plans. Through these efforts, we anticipate that FAPI PET/CT will provide lung cancer patients with more personalized and effective treatment options in the future, ultimately leading to improved prognosis and quality of life.

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