Systematic Reviews

RESEARCH

Open Access

Revolutionizing cancer diagnosis and dose biodistribution: a meta-analysis of [68ga] FAPI-46 vs. [18f] FDG imaging

Samaneh Abbasi[1], Mohsen Dehghani[2], Sara Khademi[3], Rasoul Irajirad[4], Zahra Pakdin Parizi[5], Mahdieh Sahebi[2], Masoumeh Sadeghi[2*], Alireza Montazerabadi[1,6*] and Meysam Tavakoli[7]

Abstract

Background Advancements in novel peptides significantly affect cancer diagnosis by targeting cancer-specific markers, thereby improving imaging modalities, such as positron emission tomography combined with computed tomography (PET/CT) for more accurate tumor detection. This systematic review and meta-analysis aimed to assess the diagnostic accuracy of [18F] Fluorodeoxyglucose (FDG) and ^{68}Ga-fibroblast activation protein inhibitor (FAPI- 46) PET/CT for early cancer detection**.**

Methods A comprehensive search was conducted in Scopus, MEDLINE, Web of Science, and Embase databases up to March 28, 2024, using MeSH keywords. Titles and abstracts were screened to identify studies on hybrid [68Ga] FAPI- 46 and [18F] FDG, followed by a detailed full-text evaluation. Only cohort or cross-sectional studies published in English, focusing on the clinical diagnosis of cancer patients, were included, while reviews, case reports, conference proceedings, and abstracts were excluded. Random-effects meta-analysis was used for the estimation of pooled specificity and sensitivity with 95% confidence intervals (CIs). In addition, the heterogeneity was assessed across studies and subgroup meta-analyses for the detection rate via Stata.

Results Among the 615 retrieved studies, nine articles were incorporated in the present systematic review, with five ($n = 144$ patients) eligible for meta-analysis. For [68Ga] FAPI- 46, the pooled sensitivity and specificity compared with immunohistopathology were 0.96 (95% CI 0.84, 0.99) and 0.92 (95% CI 0.53, 0.99), respectively, with a positive likelihood ratio (LR +) of 4.41 (95% CI 1.64, 11.79) and a negative likelihood ratio (LR –) of 3.07 (95% CI 1.01, 9.37). For [18F] FDG, pooled sensitivity and specificity compared with immunohistopathology were 0.73 (95% CI 0.34, 0.93) and 0.83 (95% CI 0.57, 0.95), with an LR + of 12.73 (95% CI 1.43, 113.45) and an LR – of 0.32 (95% CI 0.11, 0.17). The pooled odds ratio for the detection rate on a per-lesion basis was 1.73 (95% CI 0.99, 3.02) for [68Ga] FAPI- 46 compared with [18F] FDG. The pooled weighted mean differences in the standardized uptake value (SUV_{max}) for primary tumor uptake and the tumor-to-background ratio (TBR) in [68Ga] FAPI- 46 vs. 18F-FDG were 4.40 (95% CI – 0.7, 9.5) and 6.18 (95% CI 1.74, 10.61), respectively. Moderate to high heterogeneity was noted because of the variations in patient selection, interpretation criteria, and scanning procedures.

Conclusions This study revealed that [68Ga] FAPI- 46 outperforms [18F] FDG in cancer diagnosis, with higher sensitivity (0.96 vs. 0.73) and specificity (0.92 vs. 0.83). [Ga] FAPI- 46 improved tumor detection with higher SUVmax

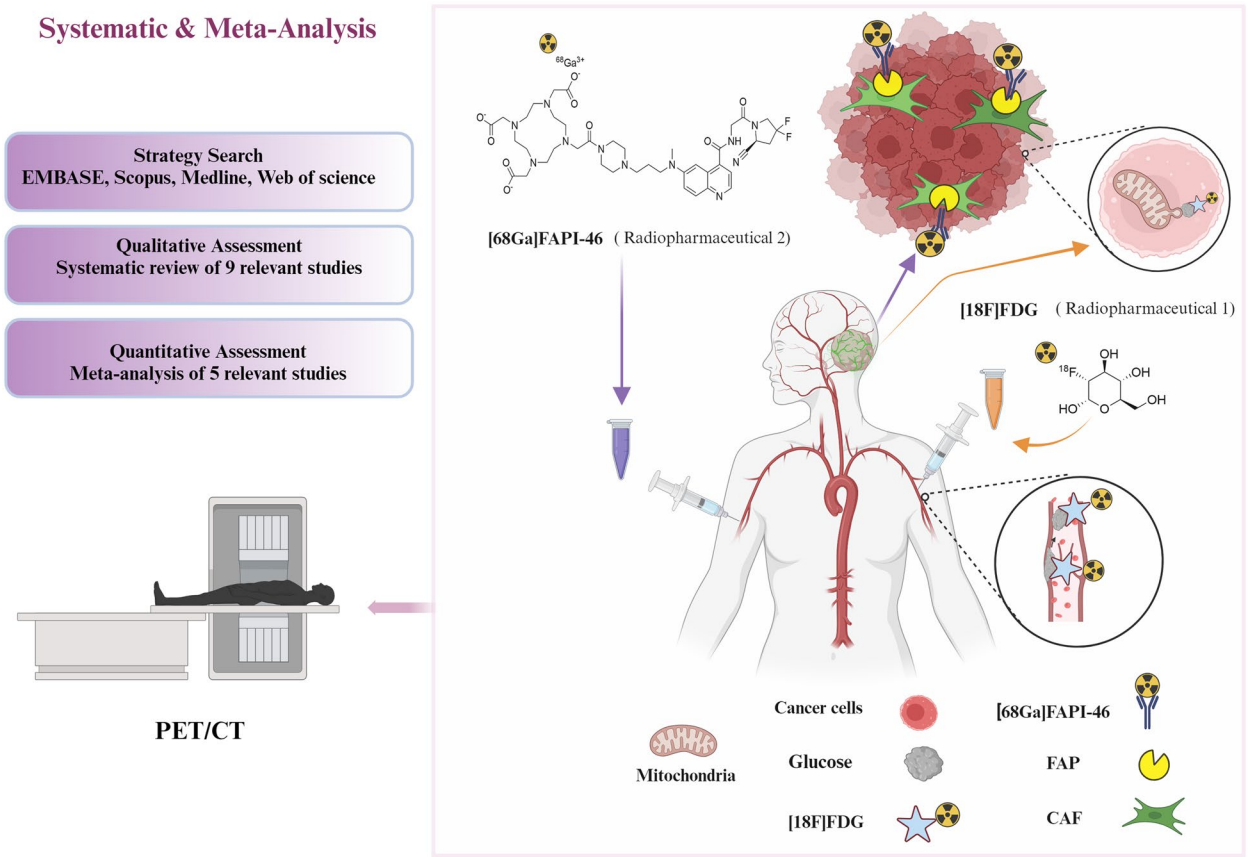
*Correspondence:
Masoumeh Sadeghi
sadeghi.masoume@gmail.com
Alireza Montazerabadi
alireza.montazerabadi@gmail.com
Full list of author information is available at the end of the article

and TBR. While FDG had a higher LR +, its lower LR – highlighted more false negatives. Accordingly, [68Ga] FAPI- 46 exhibited superior accuracy and reliability than FDG in cancer diagnosis.

Systematic review registration PROSPERO CRD 42023472270.

Keywords [68Ga] Fibroblast activation protein inhibitor (FAPI- 46), [18F] Fluorodeoxyglucose (FDG), Positron emission tomography/computed tomography (PET/CT), Cancer, Meta-analysis

Graphical Abstract



Background

Cancers, as a leading cause of death worldwide, have caused extensive research efforts to develop early and accurate diagnostic techniques. Precise diagnosis and staging are essential keys for effective disease management, which typically utilize computed tomography (CT) [1–3], magnetic resonance imaging (MRI) [4, 5], or nuclear medicine imaging, like positron emission tomography (PET) [6–8] using different radiopharmaceuticals, such as fluorine- 18 (18F)-labeled fluorodeoxyglucose (FDG) [9–12]. The development of PET scans has significantly advanced cancer diagnosis due to focusing on cellular metabolism [13–16]. Cancer cells characterized by increased glucose metabolism, exhibit higher uptake of [18F] FDG compared to non-cancer cells. This enhanced uptake facilitates the detection and visualization of tumors through PET imaging, providing valuable diagnostic insights [17–20]. Accordingly, [18F] FDG is widely recognized as a key radiotracer in cancer imaging, aiding in the identification and staging of various malignancies [21–24]. The whole-body [18F] FDG-PET/CT imaging also highlights metabolic differences in lung cancer patients, distinguishing those with and without cancer-associated cachexia and revealing systemic metabolic alterations in cachectic individuals [19, 25]. Moreover, the effectiveness of [18F] FDG PET/CT in detecting

unknown primary cancers is influenced by the distribution of metastatic sites [26, 27]. Various FDG-PET/CT parameters have demonstrated its potential as prognostic indicators of treatment outcomes in patients with oropharyngeal squamous cell carcinoma [28, 29]. On the other hand, [18F] FDG PET/CT has some drawbacks, such as false positives, which are caused by inflammation, and limited sensitivity in detecting tumors with low glycolytic activity. Additionally, the presence of high physiological uptake can obscure the visibility of lesions [30–32].

The above limitations of [18F] FDG have led to the exploration of more effective pharmaceutical-based imaging agents. Among these, [68Ga] fibroblast activation protein inhibitor- 46 ([68Ga] FAPI- 46) has significantly attracted attention due to its enhanced targeting capabilities as [68Ga] FAPI- 46 has the ability to significantly increase the accuracy of initial cancer staging and the detection of biochemical recurrence [8, 33]. [68Ga] FAPI- 46 binds to fibroblast activation protein (FAP), which is overexpressed in the stromal components of over 90% of epithelial carcinomas. It has emerged as a valuable tracer in oncology in order to improve diagnostic accuracy and treatment outcomes [34–36]. FAPs are highly expressed by cancer-associated fibroblasts in different cancer types, while their expression remains relatively low in normal tissues. The application of [68Ga] FAPI- 46 in diagnostic imaging, via PET/CT scans, enhances tumor detection [37–39]. Additionally, [68Ga] FAPI PET/CT exhibits greater sensitivity than [18F] FDG PET/CT across different cancers [40–44]. FAPI PET is also able to accurately delineate head and neck squamous cell carcinoma (HNSCC) for radiotherapy planning [45–47], leading to high detection rates across numerous solid tumors, including lung, head and neck, urogenital, gastric, colorectal, and pancreatic cancers [45, 48–51]. Furthermore, [68Ga] FAPI- 46 PET/CT detects more primary lesions, local recurrences, distant metastases, and nodal metastases than [18F] FDG PET/CT [52–54].

These findings suggest that FAPI- 46 may enhance cancer diagnosis and facilitate personalized treatment planning. Modern diagnostic techniques are strongly dependent on advanced imaging modalities, such as PET/CT and PET/MRI, due to the availability of detailed anatomical and functional information [55–57]. As a result, FAPI is cancer specific, leading to improved diagnostic accuracy and applicability across a wider range of cancers [58–60].

Gao C et al. conducted a meta-analysis to compare [68Ga] FAPI with [18F] FDG PET/CT on gastric malignancy and presented that [68Ga] FAPI was significantly more sensitive than [18F] FDG in evaluating primary tumors, distant metastases, and lymph nodes. However, no significant difference was observed in the lymph node metastasis specificity [61]. Liu X et al. conducted a study comparing [68Ga] FAPI with [18F] FDG PET/CT and revealed that FAPI had a significantly higher detection rate for primary tumors compared to FDG [62]. The meta-analysis by Gege Z et al., showed that [68Ga] FAPI had superior sensitivity in detecting peritoneal metastasis (PM) compared to those of [18F] FDG PET/CT [63]. Although some systematic and meta-analytical studies have compared [68Ga] FAPI with [18F] FDG for diagnosing specific cancers, such as colorectal cancer, primary digestive system cancers, lung cancer, and pelvic cancers, a comprehensive analysis across all cancer types has yet remained lacking. Notably, no systematic or meta-analytical study has yet focused on comparing [68Ga] FAPI- 46 with [18F] FDG across all cancer types [62, 64–68].

This study hypothesizes that [68Ga] FAPI- 46 will outperform [18F] FDG in diagnostic sensitivity and specificity for early cancer detection using PET/CT. This hypothesis is based on the premise that [68Ga] FAPI-46, due to its higher specificity for tumor-associated fibroblasts, will provide superior tumor visualization and more accurate identification of cancerous lesions, particularly in malignancies with limited [18F] FDG uptake. Additionally, we aim to analyze biodistribution metrics, such as SUV and TBR, to determine whether [68Ga] FAPI- 46 offers improved differentiation between malignant and healthy tissues. Lastly, this study seeks to evaluate various diagnostic factors, including patient characteristics, injected doses, and imaging time points, to provide comprehensive insights into the effectiveness of these radiotracers.

Methods

Protocol and registration

This systematic review and meta-analysis was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [69] and also registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023472270) [17]. Further, the ethical approval and informed consent were not applicable and usable for the current article.

Search strategy

A comprehensive search was performed across the Scopus, MEDLINE, Web of Science (WOS), and Embase databases up to March 28, 2024. The search incorporated terms “FAPI- 46” or “FAPI46” or “FDG” or “18F” or “68Ga” or “Ga68” AND “Cancer” or “Neoplasm” AND “PET/CT” developed using Boolean operators and relevant keywords from the MeSH databases. An example of search strategy in the MEDLINE was as

follows: (FAPI- 46]) OR FAPI46 [Title/Abstract]) OR FDG [MeSH Terms]) OR 18F [MeSH Terms]) OR 68Ga [MeSH Terms]) OR Ga68 [Title/Abstract]) AND (PET/CT [MeSH Terms]) AND Cancer [Title/Abstract]) OR (Neoplasm [MeSH Terms]), for more information, you can check the supplementary (Supplementary file 1: Table S1). For more information, please see the Supplementary file 1: Table S1. Additionally, references from pertinent studies were manually checked to ensure comprehensive coverage. After removing duplicates, two independent reviewers (SA and MS) screened the titles and abstracts. Inter-rater reliability for screening studies between two reviewers was calculated using Cohen's kappa to be 0.87, which is interpreted as almost perfect agreement. Discrepancies were also resolved with a third reviewer, who serves as a mediator.

Inclusion criteria were as follows: (1) studies had to be either cohort (retrospective or prospective) or cross-sectional in design, (2) patients diagnosed with cancer using [68Ga] FAPI- 46 and [18F] FDG, based on established guidelines or an oncologist's diagnosis, (3) studies were published in English, and (4) studies had clinical, diagnostic, or targeting specialized insights. The studies were included if sensitivity or specificity, or both were elaborately reported. Reviews, letters, case reports, systematic reviews, book chapters, conference papers, and studies that did not focus on both [68Ga] FAPI- 46 and [18F] FDG or failed to specify the FAPI type were excluded from the review.

The information from each article was extracted in two parts: general information (the first author's name, publication year, country, age, gender, and study population) and specific details (patient recruitment guidelines, sample sources, area under the curve [AUC], true positives [TP], true negatives [TN], false positives [FP], false negatives [FN], sensitivity, and specificity). Two reviewers (SA and MS) independently extracted data from each study. Following this, two authors reviewed and discussed the articles to ensure the accuracy of the extracted information. In the final stage, the selected articles were summarized, and the data were compiled. All disagreements between the two reviewers were addressed to reach a consensus.

Quality assessment

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool can assess the quality, reliability, and validity of diagnostic accuracy studies, helping researchers and clinicians evaluate the trustworthiness of study findings for future research or clinical practice, respectively. In the current study, two independent reviewers (MS and MD) assessed the risk of bias and applicability concerns using QUADAS- 2, in accordance with the Cochrane Collaboration guidelines, to ensure the methodological quality of the included studies [70].

Each study was evaluated for the patient selection, performance of the index test as well as the reference test, and timing and flow with criteria rated as "yes," "no," or "unclear," based on whether the requirement was met, unmet, or not explicitly addressed. Studies were further categorized as having "low," "high," or "unclear" for risk of bias and for concerns regarding applicability.

Statistical analysis

Statistical analyses were conducted using RevMan 5.3 (Cochrane, USA) and Stata version 17.0 (Stata Corp., College Station, TX, USA). The pooled sensitivity and specificity of [68Ga] FAPI and [18F] FDG PET/CT were calculated and compared, with 95% confidence intervals (CI) by random-effects meta-analysis and with forest plots for visual inspection. These measures were quantitatively combined for the generation of a summary receiver operating characteristic (SROC) curve with 95% confidence and prediction regions. Also, the positive likelihood ratio (LR +; the probability that a person with the cancer tested positive/probability that a person without cancer tested positive) and negative likelihood ratio (LR −; the probability that a person with cancer tested negative/probability that a person without cancer tested negative) were calculated to assess the diagnostic test. Heterogeneity, which is related to diagnostic performance variability, like LR + and LR − across different studies, was evaluated using the Q test and I^2 statistics ($I^2 = 0\%$ indicates no observed heterogeneity and $I^2 \geq 50\%$ indicates substantial heterogeneity) [71, 72]. Meta-regression and subgroup meta-analyses were not performed, and it was not possible to assess the source of observed heterogeneity across studies because small numbers of studies were included in each meta-analysis, which reduces the power of the meta-analyses models of diagnostic performance. Subgroup meta-analysis was performed using pooled odds ratio for detection rate/detection efficacy on a per-legion basis in [68Ga] FAPI- 46 versus [18F] FDG PET/CT. Meta-analyses of weighted mean difference were also carried out for standardized uptake value (SUV_{max}) and standardized tumor-to-background ratio for primary tumor uptake and metastasis uptake. The assessment of publication bias was not conducted due to the limited number of studies included in the analysis. Sensitivity analyses were carried out to identify any individual study that might significantly influence heterogeneity and to evaluate the robustness of the findings.

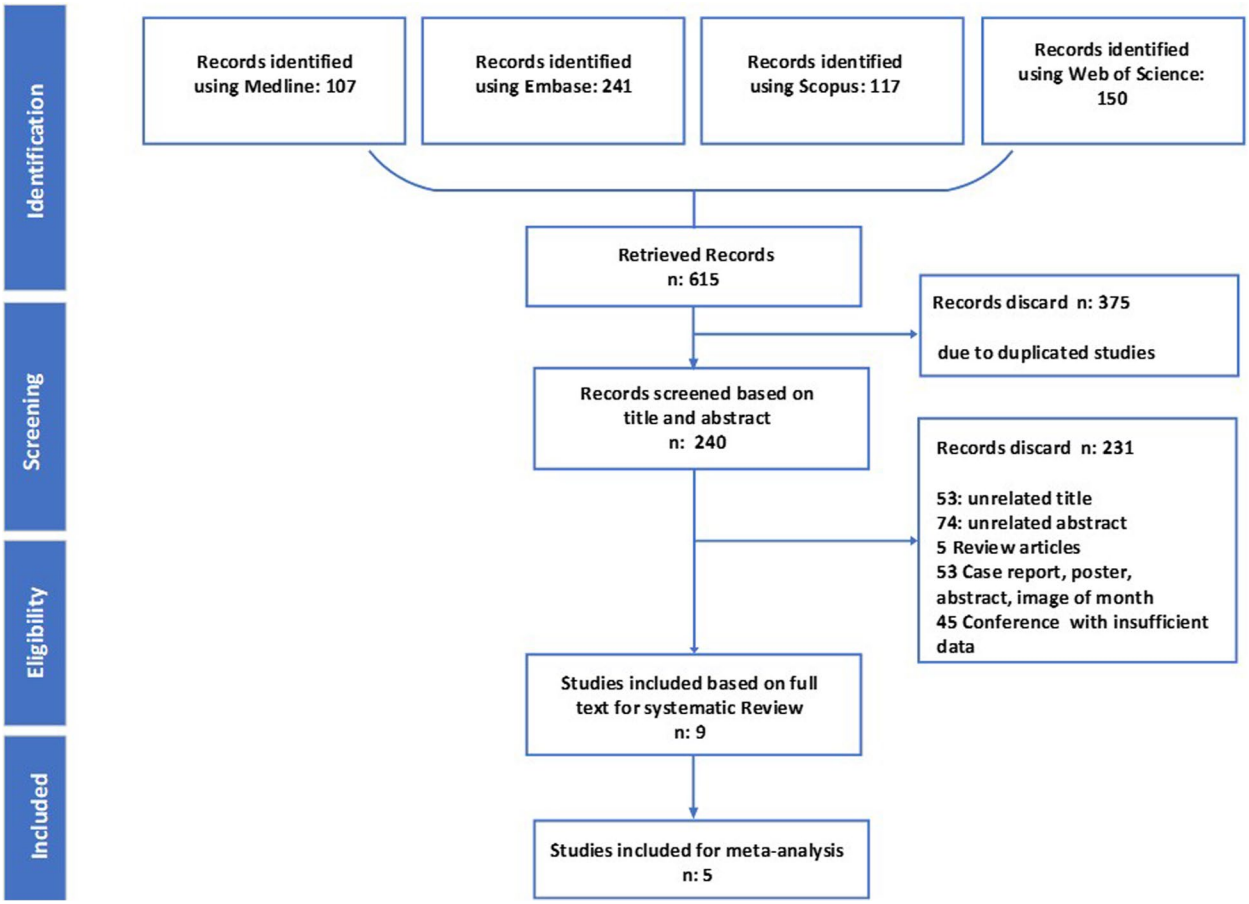


Fig. 1 PRISMA flowchart for selection of studies

Results

Literature search

Figure 1 illustrates the study selection process based on the PRISMA flow diagram. A comprehensive and in-depth search was performed in four major databases, MEDLINE ($n=$ 107), Scopus ($n=$ 117), Web of Science ($n=$ 150), and EMBASE ($n=$ 241), up to March 28, 2024, resulting in 615 studies. After removing duplicates, 240 unique articles remained for title and abstract screening. At this stage, 231 articles were excluded, including irrelevant studies, reviews, book chapters, and conference abstracts. The full texts of the remaining 9 articles [73–81] (197 patients) were then evaluated for eligibility and deemed eligible for qualitative analysis (systematic review). However, four of the studies were not included into the meta-analysis due to insufficient data. Ultimately, five studies, encompassing 144 patients diagnosed using both [68Ga] FAPI- 46 PET/CT and [18F] FDG PET/CT, were included in the meta-analysis. The patients' mean age ranged from 48.1 to 72.5 years. The primary objective of these studies was to compare the diagnostic performance of [68Ga] FAPI- 46 and [18F] FDG via PET/CT scans for early cancer detection.

Studies and patients' characteristics

The main characteristics were extracted through a review of the published included articles (Table 1). Figure 2A shows that the nine studies included in this review were conducted across various countries, with the majority (55.5%) in Germany. The remaining studies were conducted in Thailand (22.2%), Korea (11.1%), and China (11.1%). Figure 2B illustrates that, of the nine studies, 44.4% were published in "The Journal of Nuclear Medicine", 22.2% in "Molecular Imaging and Biology", 11.1% in "Research Square Journal", 11.1% in "Clinical Nuclear Medicine", 11.1% in "European Journal of Nuclear Medicine and Molecular Imaging", and 11.1% in "Asia Ocean Journal of Nuclear Medicine and Biology". Thus, Germany and "The Journal of Nuclear Medicine" were the most prominent contributors to the included studies. The systematic review consisted of three prospective studies, five retrospective studies, and one single-center exploratory comparative imaging study.

Table 1 Main characteristics of the included studies

Autor, year [Ref]	Country	Study design	Male/female (no.), mean age	Cancer type	[18F] FDG, sample size	[18F] FDG, injected activity (MBq)	[18F] FDG, imagining time (min)	[68Ga] FAPI-46 Sample size	[68Ga] FAPI-46 Injected activity (MBq)	[68Ga] FAPI-46 Imagining time	Initial staging (S) Restaging (R) %	Grading High (H) Low (L) %	Cancer status %
Kessler. L, 2022 [73]	Germany	Prospective	24/23 48.1	Bone and soft-tissue sarcomas	43	214 ± 102	60	43	144 ± 36	10	S: 36.2 R: 42.6 Localization before local therapy: 21.3	H: 74.5 L: 10.6 No applicable: 14.9	NR
Promteangtrong. C, 2022 [74]	Thailand	A single-center exploratory comparative-imaging	27/13 56.67	Head and neck	40	181.3	60	40	140	60	S: 30 Re:70	NR	Primary 88.88 Lymph node:5.5 Lung metastas:5.5
Roth. K.S, 2022 [75]	Germany	Retrospective	6/0 72.5	Head-and-neck, and esophageal cancer	6	272 ± 27.8	81.3 ± 38.1	6	177 ± 35.7	18.2 ± 20.1	NR	NR	NR
Siripongsatian D, 2022 [76]	Thailand	Retrospective	21/6 68	Liver	27	181.3	60	27	181.3	60	S: 22 R:67 Suspected recurrence:11	NR	NR
Wegen S. 2022 [77]	Germany	Retrospective	12/3 66.0	Head and neck	15	263	NR	15	147	NR	NR	NR	Primary: 31.25 Nodal meta:47.9 Visceral meta:14.5 Bone meta:6.25
Guo W, 2023 [78]	China	Retrospective study	0/28 52.0	Breast	28	259	NR	28	154	NR	NR	NR	NR
Pabst. K.M, 2023 [79]	Germany	Prospective	4/6 55.5	Cholangiocarcinoma	9	317 [266, 344]	63 [54, 80]	10	89 [79, 128]	15 [10, 38]	NR	NR	Primary 22.72 Node meta 50 Distance Meta 22.72
Wegen, S. 2023 [80]	Germany	Retrospective	0/7 51.7	Cervical	7	234 ± 37.8	71.5 ± 17	7	152 ± 24	50 ± 23	NR	NR	NR
Kang. Y. K, 2024 [81]	Korea	Prospective	16/7 66.0	Lung	23	9.8	60	23	185	60	NR	NR	NR

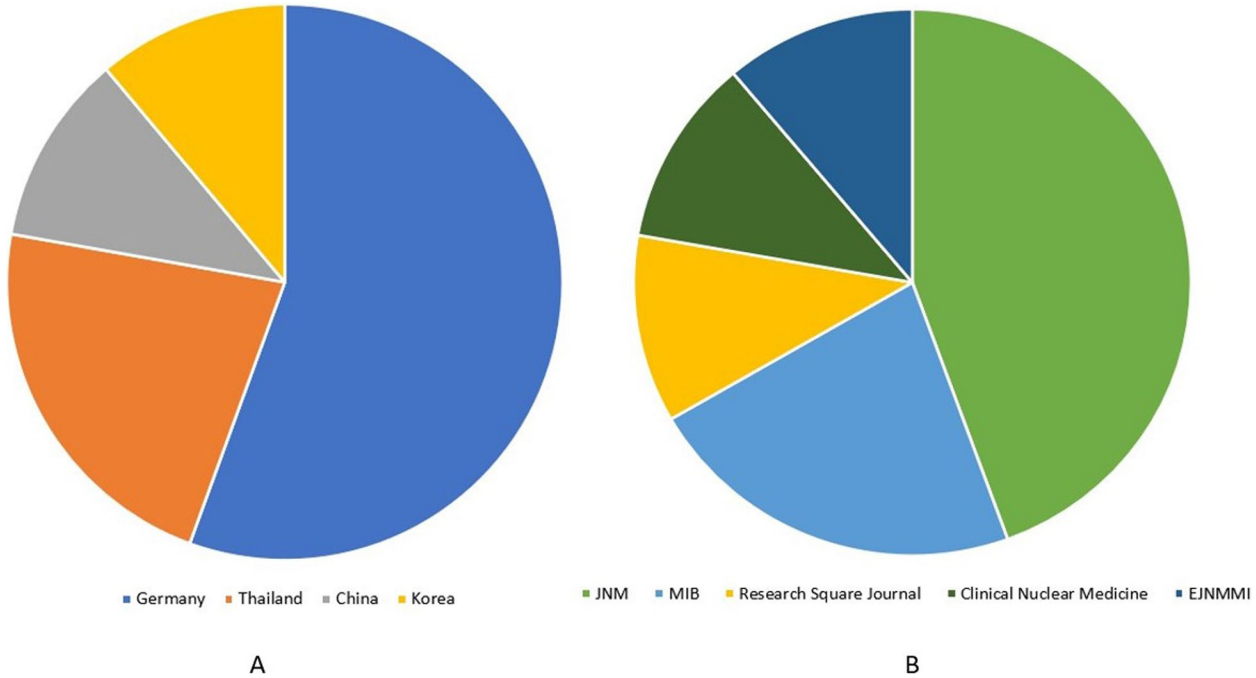


Fig. 2 The charts of countries and publishers

Technical aspects

The technical aspects of [18F] FDG-PET/CT and [68Ga] FAPI- 46 PET/CT from the nine studies are also summarized in Table 1. The administered activity of [18F] FDG varied considerably, ranging from approximately 180 to 320 MBq, while the activity of [68Ga] FAPI- 46 ranged from 80 to 190 MBq. Imaging acquisition times for both tracers were between 10 and 90 min. Most scans concentrated on head and neck cancers; however, other types, including breast, liver, cervical, and lung cancers, were also investigated. The sample sizes of the selected studies varied (6 to 43.) In the detailed assessment of these nine articles to compare the two scanning methods, histopathological diagnosis was considered the gold standard.

Methodological quality of the included studies

Table 2 presents the QUADAS- 2 assessment for all 9 included studies. In the patient selection domain, 44% (4/9) of studies revealed a high risk of bias, due to study design limitations, such as the lack of consecutive or random sampling. Also, the flow and timing domain presented a high risk of bias in 44% of studies, due to incomplete information or results. However, 77% (7/9) of the studies were classified because of a low risk of bias, as [68Ga] FAPI- 46 or [18F] FDG interpretations were blinded to the reference standard (immunohistopathology), or pre-established cutoff values were used to categorize results as positive, negative, or indeterminate. Regarding applicability concerns, the majority

Table 2 Quality assessment of included studies using QUADAS- 2 tool [73–82]

	Risk of bias				Applicability concerns		
First author, year	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
[73]	+	+	+	–	+	+	+
[74]	+	+	+	–	+	+	+
[75]	–	–	+	–	?	?	+
[76]	–	+	+	+	+	+	+
[77]	–	+	+	+	+	+	+
[78]	+	?	–	+	+	+	+
[79]	+	+	?	–	+	+	?
[80]	–	?	+	+	+	+	+
[81]	+	?	+	+	+	+	+

of studies (88%, 8/9) were rated with low concerns for patient selection, index test performance, and reference test performance, with no significant issues identified. In summary, regarding the overall judgment, 8 studies (88%) were judged as "at risk of bias" and one study was rated "unclear risk of bias". Also, only two studies were judges as having "concerns regarding applicability" while seven studies (77%) were considered as "low concern regarding applicability" (Fig. 3).

Main findings of qualitative synthesis

This systematic review aimed to compare the diagnostic accuracy of [18F] FDG PET/CT and [68Ga] FAPI- 46 PET/CT based on histopathological findings. The [68Ga] FAPI- 46 has recently emerged as a promising alternative to [18F] FDG, particularly for tumors with high fibroblast content or low metabolic activity [64, 82, 83]. However, [18F] FDG remains effective for cancers with high glucose metabolism, its diagnostic utility is limited by non-specific uptake in normal tissues and inflammatory sites.

According to the findings, only two studies (22.2%) assessed tumor stage and grade. Additionally, cancer characteristics, such as a primary tumor or metastatic status, were reported in 33.33% [74, 77, 79] of the studies reviewed. The conclusions of the included studies are reported in Table 3.

Our systematic review provides compelling evidence that [68Ga] FAPI- 46 PET/CT demonstrates superior diagnostic accuracy compared to [18F] FDG PET/CT across several malignancies, including sarcoma, breast cancer, cholangiocarcinoma, HNSCC, and non-small cell lung cancer (NSCLC). The utilization of [68Ga] FAPI- 46 is associated with enhanced sensitivity and specificity in the detection of both primary and metastatic lesions. Notably, the uptake of [68Ga] FAPI- 46 is particularly pronounced in tumors characterized by high expression of FAP within the tumor stroma, such as grade 3 cholangiocarcinoma. In general, the results present that [68Ga] FAPI- 46 PET/CT, as a promising imaging modality, can improve diagnostic precision in different cancers.

Quantitative synthesis (meta-analysis)

The included studies for the quantitative analysis

The five studies included in the meta-analysis [73, 74, 76, 80, 81] evaluated the diagnostic performance of both [68Ga] FAPI- 46 PET/CT and [18F] FDG-PET/CT for cancer detection. These studies provided TP, TN, FP, and FN, which were used to calculate sensitivity and specificity, key metrics for assessing diagnostic accuracy. Additionally, the studies that reported detection rates and dose biodistribution were further analyzed, and a meta-analysis was conducted for these specific parameters (Table 4).

Meta-analysis of [68Ga] FAPI- 46 for cancer diagnosis

Five studies [73, 74, 76, 80, 81] assessed the diagnostic accuracy of [68Ga] FAPI- 46 and [18F] FDG PET/CT in cancer detection. Figure 4 presents a forest plot displaying the sensitivity and specificity of the [68Ga] FAPI- 46 studies. The pooled sensitivity was 0.97 (95% CI 0.84–0.99), with the lowest sensitivity at 0.75 (95% CI 0.19–0.99) and the highest, observed in two studies, reaching 1.00 (95% CI 0.79–1.00 and 0.82–1.00). The pooled specificity was 0.92 (95% CI 0.53–0.99), with the lowest specificity at 0.50 (95% CI 0.01–0.99) and the highest, reported in three studies, at 1.00 (95% CI 0.29–1.00, 0.77–1.00, and 0.03–1.00). Figure 5 also depicts the summary receiver operating characteristic (SROC) curve for [68Ga] FAPI-46, with a curve approaching the upper left corner, indicating a larger area under the curve and, consequently,

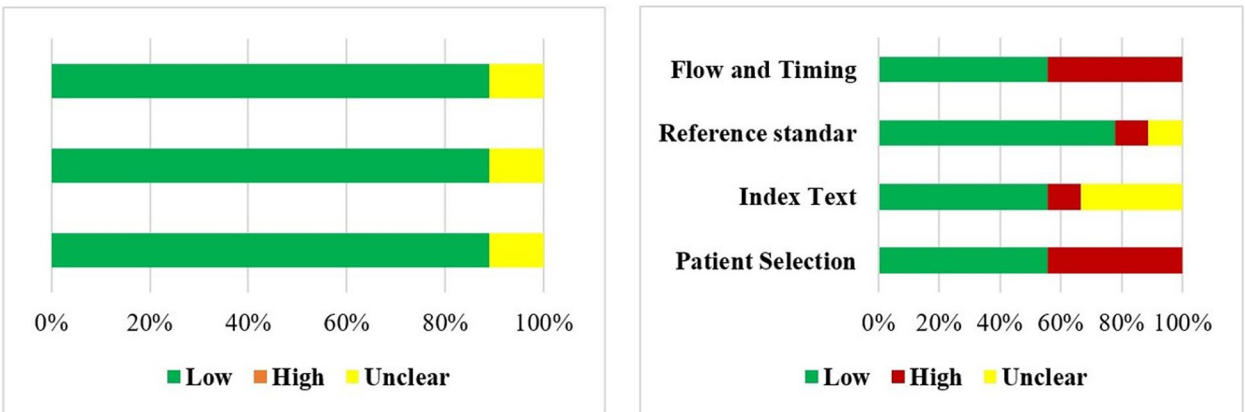


Fig. 3 Summary results of the QUADAS- 2 tool. The proportion of studies with low, high, and unclear concerns. The Proportion of studies with low, high, and unclear risk regarding applicability of bias

Table 3 The findings of included studies

Ref	Conclusion	Ref	Conclusion
[73]	High accuracy and the rate of detection for [68Ga] FAPI- 46 PET than [18F] FDG PET in sarcoma patients	[78]	The superiority of [68Ga] FAPI- 46 PET/CT to [18F] FDG for diagnosing metastatic along with primary breast cancer, with higher uptake in critical areas
[74]	Strong concordance and comparable diagnostic performance [68Ga] FAPI-46 PET to [18F] FDG PET/CT for recurrence detection as well as first staging of head and neck squamous cell carcinoma (HNSCC) patients	[79]	The superior radiotracer uptake and lesion detection of [68Ga] FAPI- 46 in grade 3 cholangiocarcinoma, correlating with high FAP expression in tumor stroma
[75]	The high potential of dual-tracer 18F-FDG/[68Ga] FAPI- 46 PET/CT for superior sensitivity compared to [18F] FDG PET/CT alone	[80]	The detection of nodal metastasis detection using [68Ga] FAPI- 46 PET/CT in cholangiocarcinoma patients
[76]	The combination of [68Ga] FAPI- 46 PET/CT with PET/MRI for superior detection of hepatic malignancies compared to [18F] FDG PET/CT or MRI alone	[81]	The enhancement of preoperative mediastinal nodal staging using [68Ga] FAPI- 46 PET/CT in NSCLC by improving sensitivity and reducing false positives, potentially lowering the need for invasive procedures
[77]	The lesion detection of [68Ga] FAPI-46 PET/CT for head and neck cancers (HNCs)		

Table 4 The findings of the included studies in meta-analysis

Ref	Cancer type	Patient No	Key points
[73]	Bone/soft-tissue sarcomas	57	Assessing 68Ga-FAPI uptake and FAP expression, detection rate, PPV, and inter-reader reproducibility
[74]	Head and Neck	40	Assessing diagnostic accuracy, standard uptake values (SUVmax, SUVmean), and tumor-to-background ratio (TBR) comparison
[76]	Liver	27	Comparing all diagnostic imaging techniques
[80]	Cervical	7	Investigating nodal staging, and comparing PET imaging findings with histopathology
[81]	Lung	23	Assessing diagnostic accuracy of 68Ga-FAPI- 46 for nodes, visual as well as quantitative analysis

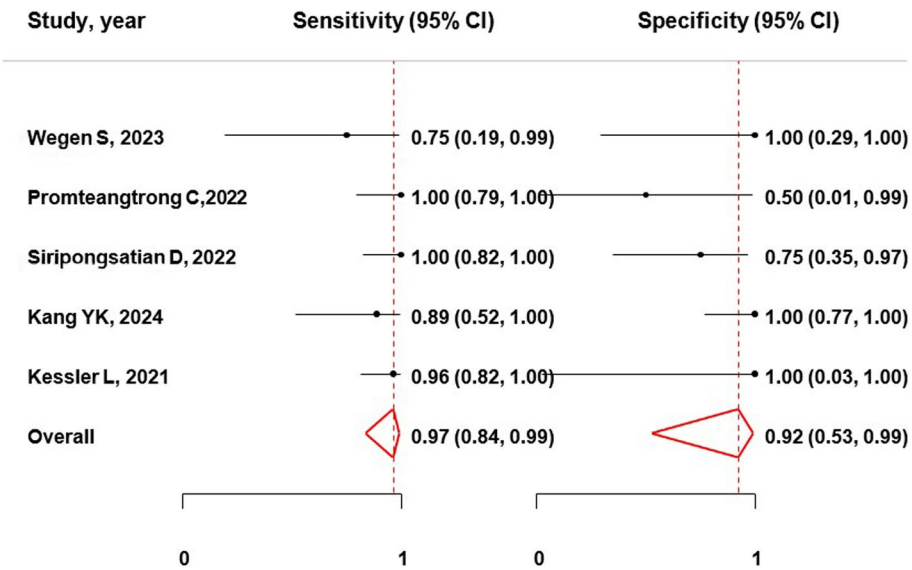


Fig. 4 Forest plots of the sensitivity and specificity of ^{68}Ga-FAPI- 46 PET/CT as a diagnostic tool

higher diagnostic precision. Based on the results, [68Ga] FAPI- 46 demonstrated low false negative and false positive rates, supporting its high diagnostic accuracy.

Meta-analysis of [18F] FDG PET/CT for cancer diagnosis

Figure 6 presents a forest plot summarizing the sensitivity and specificity of the included studies. The pooled sensitivity was 0.73 (95% CI 0.34 to 0.93), with individual sensitivities ranging from a low of 0.33 (95% CI 0.01 to 0.91) to a high of 1.00 (95% CI: 0.79 to 1.00). The overall specificity was 0.83 (95% CI 0.57 to 0.95), with values spanning from 0.50 (95% CI 0.01 to 0.99) to a maximum of 0.93 (95% CI 0.66 to 1.00). Figure 7 shows the SROC curve for [18F] FDG PET/CT. The curve, positioned further from the upper left corner, suggests a smaller area under the curve compared to [68Ga] FAPI, reflecting lower diagnostic accuracy for [18F] FDG PET/CT (Fig. 7). Table 5 presents the results of the meta-analysis comparing the two tracers, [68Ga] FAPI- 46 and [18F] FDG.

Additionally, a region-based meta-analysis was conducted to assess the diagnostic performance of [68Ga] FAPI- 46 PET/CT (Fig. 8), with a 95% CI to quantify the reliability of the findings. This analysis caused the tracer's efficacy to be evaluated in specific anatomical regions, such as the head and neck, and the liver, enhancing the detection of malignancies across various sites. The pooled sensitivity was 0.94 (95% CI 0.82, 0.98), and the specificity was 0.89 (95% CI 0.79, 0.95). Furthermore, the SROC curve reinforces the high diagnostic accuracy of [68Ga] FAPI- 46 PET/CT, particularly in identifying primary and metastatic cancer lesions.

Detection rate/detection efficacy

In this meta-analysis, the detection rates and efficiencies were assessed in three groups: primary tumors, lymph nodes, and distant metastasis. Primary tumors: the odds ratio (OR) was 1.73 (95% CI: 0.99, 3.02), indicating a potential advantage in detection rates with the heterogeneity analysis: $I^2 = 84.86\%$, and $P < 0.001$, showing significant variability among studies. For lymph nodes: the OR was 1.28 (95% CI 0.86, 1.91), representing a moderate enhancement in detection rates, and the heterogeneity

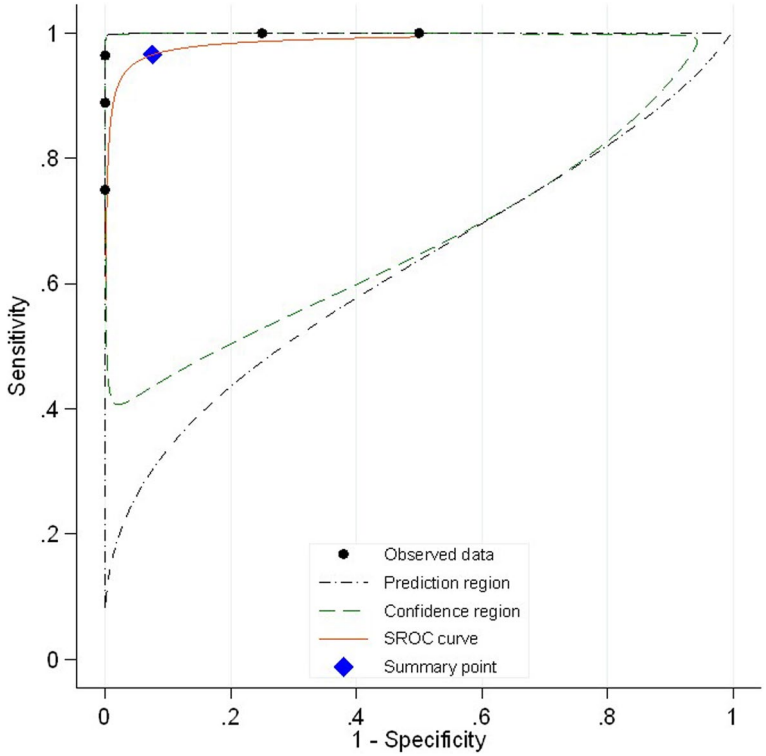


Fig. 5 Summary receiver operating curve (SROC) plot. Open circle (o) represents the false positive rate (*x*-coordinate) and sensitivity (*y*-coordinate) of individual studies. Diamond represents the summary estimate, black circle represents individual studies. Green dash represents the 95% confidence interval ([.^{68}Ga] FAPI- 46 PET/CT as diagnostic tool)

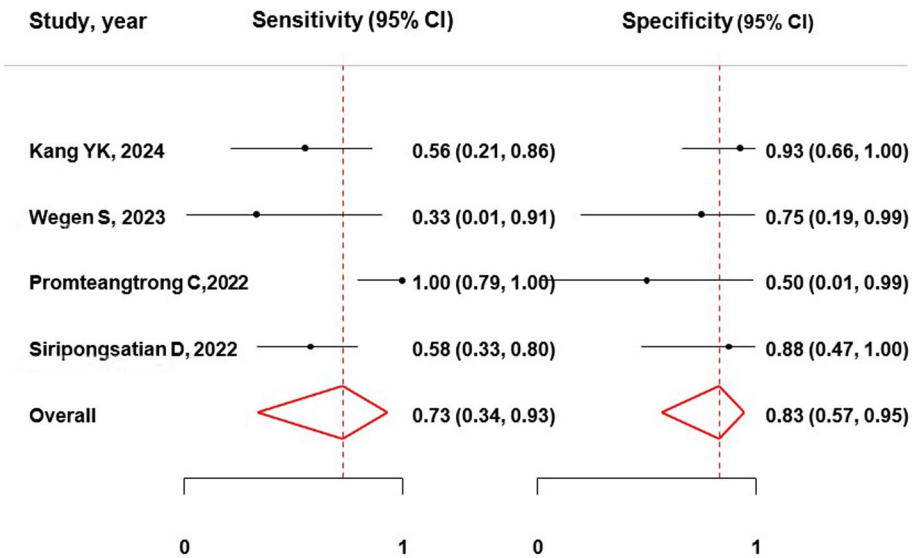


Fig. 6 Forest plots of the sensitivity and specificity of ^{18}F-FDG PET/CT as a diagnostic tool

investigation indicated $I^2 = 57.44\%$, and $P = 0.13$, indicating moderate variability (Fig. 9). Finally, in distant metastases: the OR was 1.09 (95% CI 0.96, 1.24), showing a minimal increase in detection efficiency with the heterogeneity measures: $I^2 = 0.00\%$, and $P = 0.34$, resulting in low variability among studies. Sensitivity analysis for

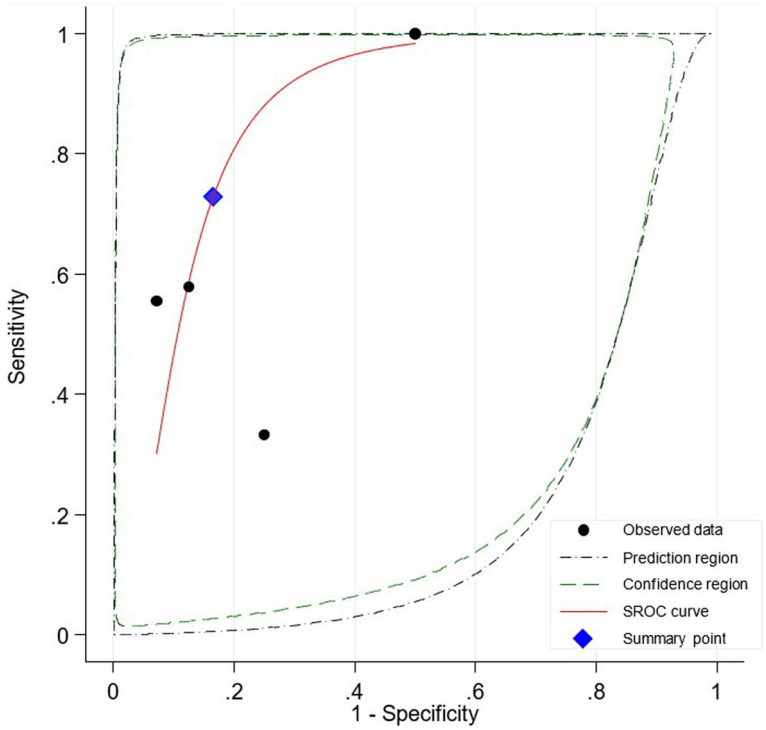


Fig. 7 Summary receiver operating curve (SROC) plot. Open circle (o) represents the false positive rate (x-coordinate) and sensitivity (y-coordinate) of individual studies. Diamond represents the summary estimate, black circle represents individual studies. Green dash represents the 95% confidence interval ([^{18}F] FDG PET/CT as diagnostic tool

Table 5 Meta-analysis of diagnostic accuracy

	[^{68}Ga] FAPI- 46 PET/CT			[18F] FDG PET/CT		
Summary	**Coef**	**SE**	**95% CI**	**Coef**	**SE**	**95% CI**
Sensitivity	0.96	0.28	0.84, 0.99	0.73	0.16	0.34, 0.93
Specificity	0.92	0.08	0.53, 0.99	0.83	0.09	0.57, 0.95
Likelihood ratio (+)	12.73	14.21	1.43, 113.45	4.41	2.21	1.64, 11.79
Likelihood ratio (–)	0.32	0.008	0.11, 0.17	0.32	0.18	0.11, 0.99
1/likelihood ratio (–)	26.74	21.40	5.57, 128.34	3.07	1.75	1.01, 9.37

detection rate of primary tumors indicated that the meta-analysis findings were robust (summary ORs, 1.24–2.16). The Pooled odds ratio for the detection rate across all lesions was almost consistent and was not varying for different tumor types. This indicates that the detection efficacy of FAPI- 46 PET/CT was greater than that of FDG PET/CT across all types of lesions, although this difference was not statistically significant.

Dose distribution

The meta-analysis results show that the comparison of primary tumor uptake between [68Ga] FAPI- 46 PET/CT and [18F] FDG PET/CT yielded a weighted mean difference (WMD) of 4.40 (95% CI −0.70, 9.50), with substantial heterogeneity ($T^2 = 33.08$, $I^2 = 89.99\%$). While [68Ga] FAPI- 46 PET/CT tends to have higher standard uptake values (SUVmax) than 18F-FDG PET/CT, the difference is not statistically significant (Fig. 10). In a sensitivity analysis excluding one study at a time, we consistently found a higher standard uptake values for FAPI- 46 PET/CT (range of summary WMDs, 2.42–5.51).

Tumor-to-background ratio (TBR), which measures radiotracer contrast between primary tumor and surrounding tissues, was assessed for blood pool, liver, and

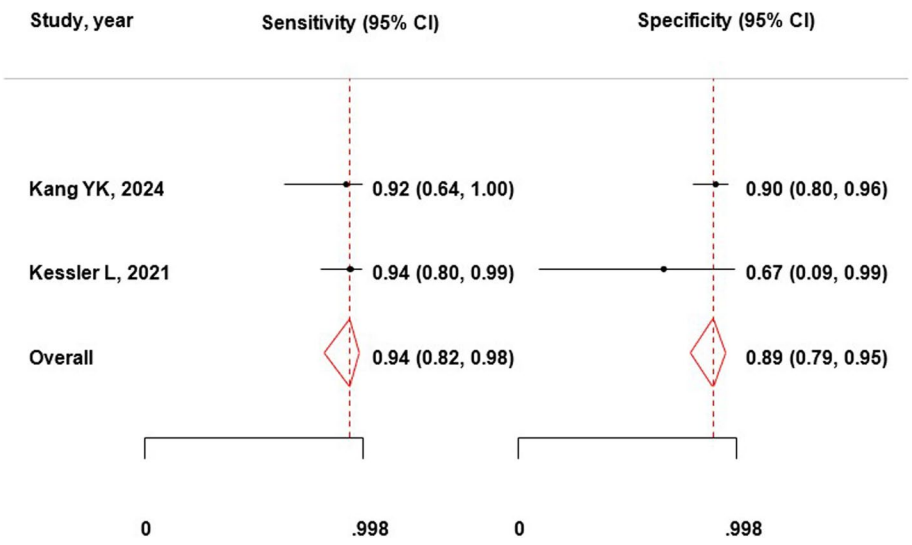


Fig. 8 Forest plots of the sensitivity and specificity of [^{68}Ga] FAPI- 46 PET/CT as a diagnostic tool. (Region base analysis)

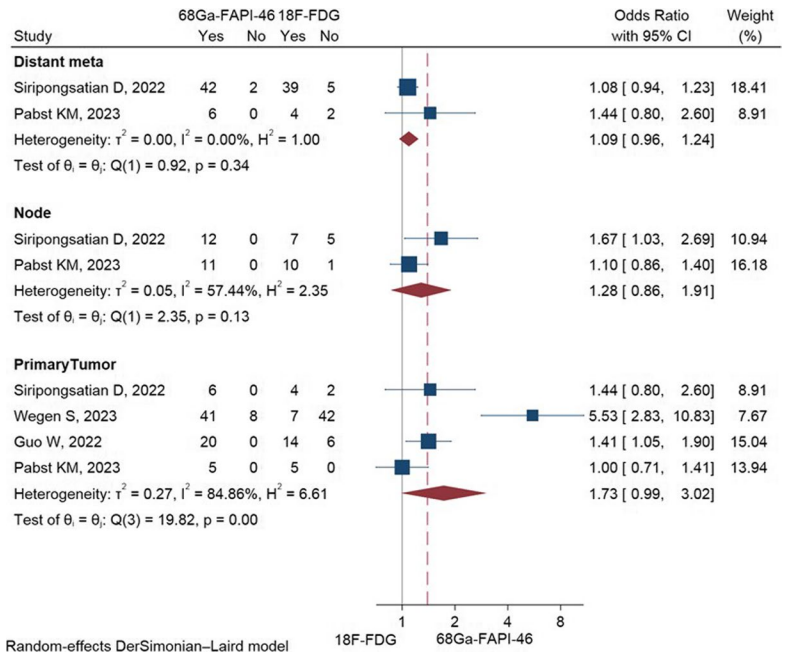


Fig. 9 Forest plot; the pooled estimation of odds ratio for detection rate/detection efficacy on a per-legion basis in [^{68}Ga] FAPI- 46 PET/CT vs. [18F] FDG PET/CT

muscle. In the blood pool, the WMD was 5.51 (95% CI 1.13, 9.89) with significant heterogeneity (I^2 = 76.95%), indicating that [68Ga] FAPI- 46 PET/CT likely has a higher TBR than [18F] FDG PET/CT. Liver analysis showed a WMD of 12.32 (95% CI: 4.58, 20.07), also with high variability (I^2 = 78.29%) (Fig. 11). Robustness of the findings and meta-analysis model was confirmed in sensitivity analysis of TBR for blood pool (range of summary WMDs, 2.96–6.79) and liver (range of summary WMDs, 8.43–17.95).

Since heterogeneity was considerable and significant in most meta-analyses, it was not possible to perform subgroup meta-analysis or meta-regression to assess the potential sources of inconsistency among studies because small numbers of studies had included in each meta-analysis. Nevertheless, variations in patient selection,

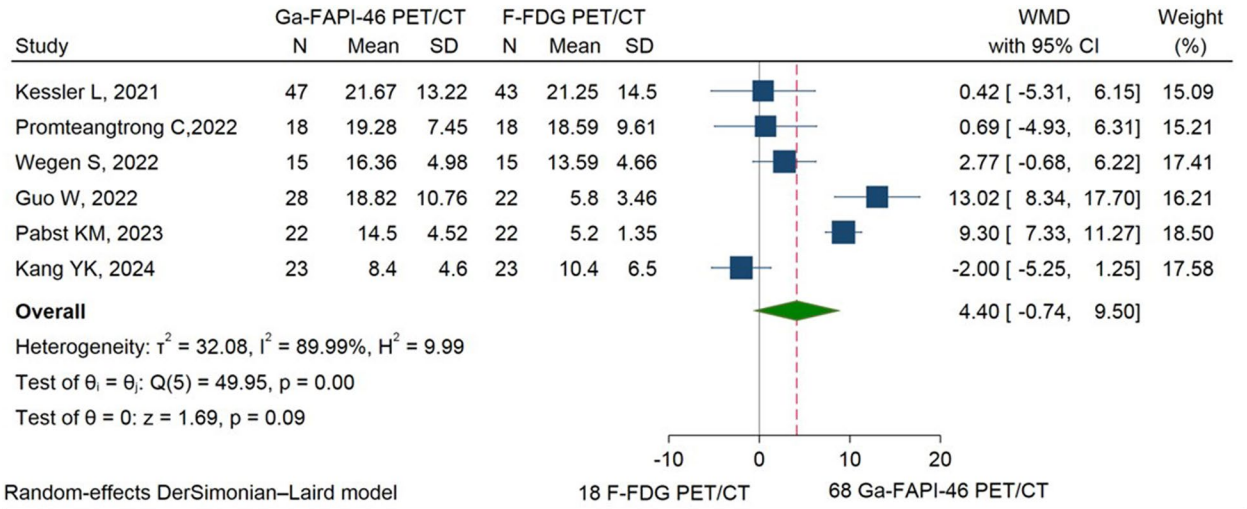


Fig. 10 Forest plot; the pooled weighted mean difference of standardized uptake value (SUVmax) for primary tumor uptake in ^{68}Ga-FAPI- 46 PET/CT vs. 18F-FDG PET/CT. [68Ga] FAPI- 46 PET/CT had higher (but not statistically significant) standard uptake values (SUVmax) than 18F-FDG PET/CT

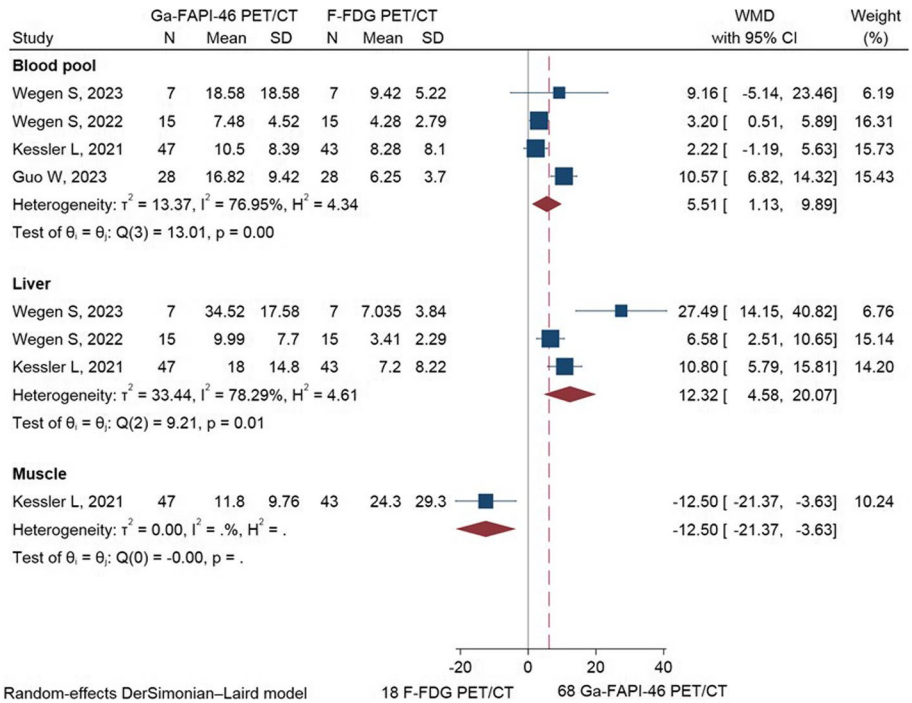


Fig. 11 Forest plot; the pooled weighted mean difference of standardized tumor-to-background ratio (TBR) for primary tumor uptake in [68Ga] FAPI- 46 PET/CT vs. [18F] FDG PET/CT. TBR was significantly higher for [68Ga] FAPI- 46 PET/CT compared to [18F] FDG PET/CT for blood pool and liver

tumor stage, patients' gender, interpretation criteria, and scanning procedures might contribute in heterogeneity among studies.

For metastatic lesions, TBR was again higher for [68Ga] FAPI- 46 PET/CT (WMD = 5.13, 95% CI 2.40, 7.86) compared to [18F] FDG, but the heterogeneity was extremely high (I^2 = 97.41%). These findings suggest that [68Ga] FAPI- 46 PET/CT demonstrates superior TBR, particularly for metastatic lesions, but study variability is considerable (Fig. 12).

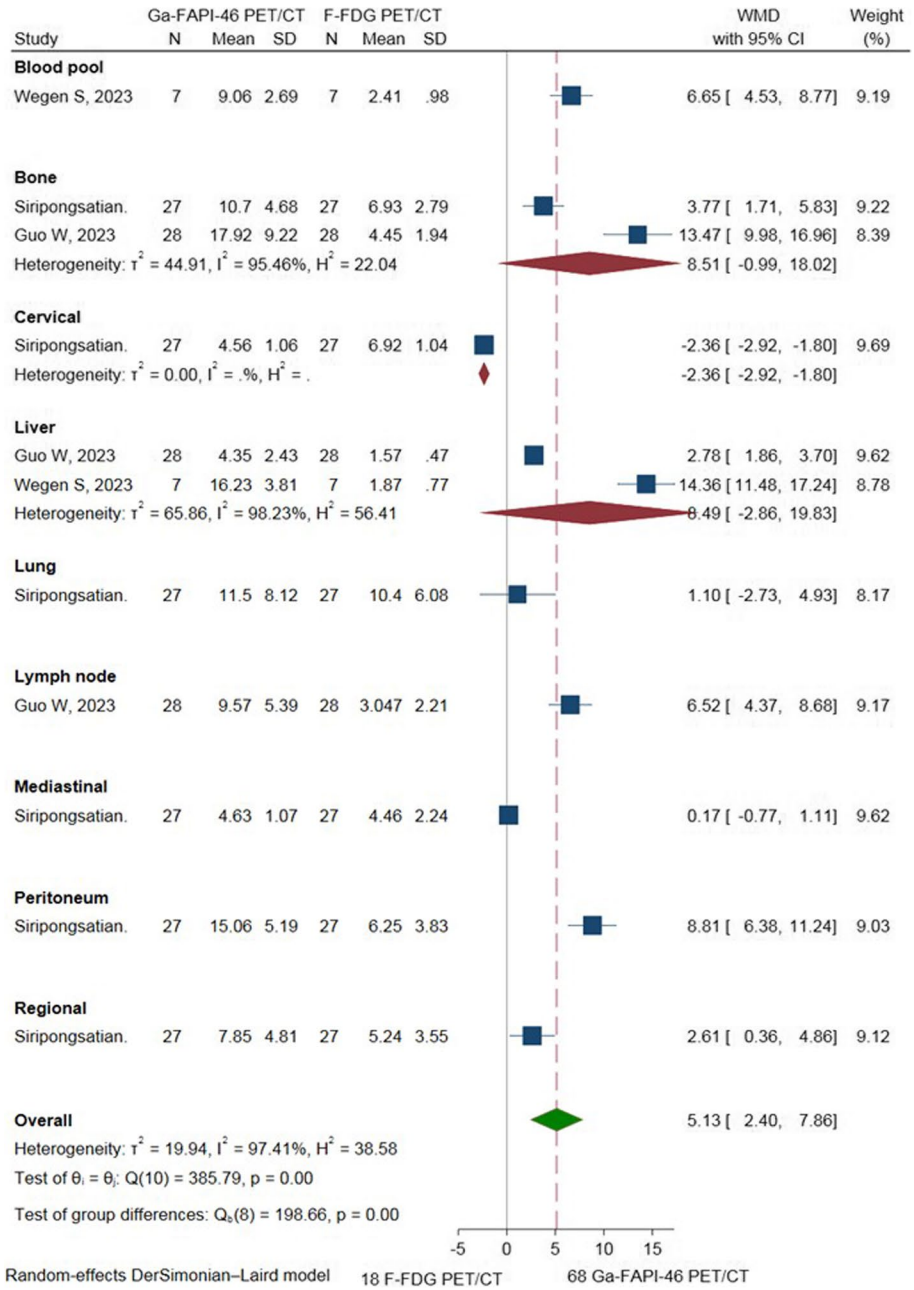


Fig. 12 Forest plot; the pooled weighted mean difference of standardized tumor-to-background ratio (TBR) for metastasis uptake in [^{68}Ga] FAPI- 46 PET/CT vs. [18F] FDG PET/CT. In overall, TBR was higher significantly for [68Ga] FAPI- 46 PET/CT (WMD: 5.13, 95% CI: 2.40, 7.86) compared to [18F] FDG for metastatic lesions

Discussion

The present systematic review and meta-analysis deeply investigate the available evidence about the diagnostic performance of [68Ga] FAPI- 46 PET/CT in comparison to [18F] FDG PET/CT for cancers. The use of [68Ga] FAPI in PET/CT imaging has been increasing in oncology [43][84, 85]. The obtained findings indicate that the sensitivity of [68Ga] FAPI- 46 is 1.33 times greater than that of [18F] FDG, leading to accurately identifying true positive cancer, particularly in early-stage cancers. Additionally, [68Ga] FAPI- 46 shows a specificity that is 1.1 times higher than that of [18F] FDG, highlighting a more accurate identification of true negative cases associated with the minimum false positives. Moreover, the region-based meta-analysis shows that [68Ga] FAPI- 46 PET/CT has better diagnostic performance with pooled

sensitivity at 0.94 and specificity at 0.89 through different anatomical regions, indicating its efficacy in malignancy detection, for primary and metastatic lesions. Regarding detection rates, primary tumors present the OR of 1.73, reflecting a significant advantage in detection efficiency, despite the considerable variability. The detection rate for lymph nodes showed a moderate increase (OR of 1.28) and variability. Contrarily, the detection of distant metastases obtained a minimal OR of 1.09, presenting slight improvement in detection efficiency as well as low variability.

For dose distribution, a higher trend in primary tumors for [68Ga] FAPI was observed than [18F] FDG PET/CT, with a 4.40 WMD. In terms of TBR that computes the contrast between primary tumors and surrounding tissues, [68Ga] FAPI- 46 revealed significantly higher values than [18F] FDG. Particularly, the TBR for the blood pool and liver showed WMDs of 5.51 and 12.32, respectively. Therefore, the TBR for [68Ga] FAPI- 46 was significantly superior to that of [18F] FDG, with a WMD of 6.18, emphasizing its improved capability to differentiate tumors from adjacent tissues; however, there is notable heterogeneity. For metastatic lesions, there has still been an advantage in TBR for [68Ga] FAPI- 46 compared to [18F] FDG. As a result, these results show that [68Ga] FAPI- 46 PET/CT has an ability to improve tumor detection and contrast against background tissues, especially for metastatic cases. However, careful interpretation and further validation are needed in larger patient cohorts due to the variability in the study results.

Compared with [18F] FDG, [68Ga] FAPI- 46 demonstrated superior uptake and lesion detection in grade 3 cholangiocarcinoma, which was correlated with high FAP expression in the tumor stroma; these findings are inconsistent with the findings of the current study [86]. Additionally, [68Ga] FAPI- 46 and [18F] FDG PET/CT provided comparable disease staging in breast cancer patients. However, [68Ga] FAPI- 46 had lower liver and blood pool uptake, leading to a TBR ratio, which may enhance lesion detection. Further validation in larger cohorts is needed to explore its potential for advanced breast cancer therapy [84]. [68Ga] FAPI- 46 PET/CT, as a revolutionary diagnostic method for breast cancer management, has superior TBR, and precise lymph node detection indicates its potential for targeted radionuclide therapies, which is in agreement with the results of the current study [87]. The [68Ga] FAPI- 46 PET/CT can enhance the detection of nodal metastasis in patients with cholangiocarcinomas (CCs) [35, 36], which is in agreement with the current results. Finally, the significance of [68Ga] FAPI PET/CT lies in its superior sensitivity, specificity, higher SUVmax, and improved dose distribution compared to [18F] FDG PET/CT. These advantages have prompted further studies, which consistently align with the findings of the present systematic meta-analysis [34, 49, 62, 88–90]. Accordingly, the present article analyzed the characteristics of [68Ga] FAPI and revealed its potential to improve diagnostic accuracy in detecting primary and metastatic lesions.

However, some meta-analyses have compared the diagnostic performance of [68Ga] FAPI and [18F] FDG PET/CT for specific cancer types, such as gastric, abdominal, colorectal, and pelvic cancers [61–67], a comprehensive analysis, which compares the performance of [68Ga] FAPI and [18F] FDG PET/CT for all cancer types remains absent. Further, despite the growing amount of research in this field, no systematic or meta-analytic study has yet directly compared [68Ga] FAPI- 46 with [18F] FDG across a wide range of malignancies. Therefore, there is a critical need to evaluate and compare the diagnostic accuracy and effectiveness of [68Ga] FAPI- 46 and [18F] FDG for various cancer types to enhance clinical decision-making. [68Ga] FAPI- 46 has a great clinical potential, particularly in oncology for radiotherapy [43, 91] since FAPI- 46 PET/CT can identify tumors, which can likely respond to therapies targeting the tumor stroma, due to its ability to image FAP expression in tumors [92]. Additionally, it facilitates the monitoring of treatment efficacy and the detection of early changes in the tumor microenvironment, showing a potential tool for optimizing personalized cancer treatment strategies.

The comparison between [68Ga] FAPI- 46 and [18F] FDG PET/CT holds important implications for clinical guidelines and future imaging protocols. Due to its higher sensitivity and specificity for FAP, [68Ga] FAPI- 46 could improve tumor detection, especially in cancers with low glucose metabolism, because of less expression of [18F] FDG. This approach can lead to more precise staging, improved treatment planning, and earlier identification of metastases and recurrences [93–95]. Moreover, the current systematic review and meta-analysis reveals that [68Ga] FAPI- 46 could improve treatment planning by enhancing tumor detection and staging, particularly in cases with ess effective [18F] FDG PET/CT since higher sensitivity may result in more precise therapy selection, optimizing surgical and radiotherapy decisions [96, 97].

The current systematic review and meta-analysis exhibits some limitations and possible future works, which may affect the interpretation of the results, as follows: (1) the analysis was constrained by a relatively small patients cohort, which may limit the generalizability of the findings by excluding some studies due to the omission of non-English publications and conference abstracts, potentially leading to a selection bias, (2) most included studies employed a case–control design, which could introduce inherent biases and confounding variables.

Accordingly, this small sample size can compromise the statistical power and robustness of the overall results, and (3) during the quality assessment, half of the studies were rated as high risk of bias, especially for domains of patient selection and flow and timing, which may also affect the reliability of the findings. Nonetheless, despite these limitations, the clinical implications of the findings remain significant, underscoring the diagnostic potential of [68Ga] FAPI PET/CT in oncology. To address the limitations of this study, future research should focus on expanding the patient population and including non-English studies and conference abstracts to minimize selection bias. Additionally, prioritizing prospective cohort studies or randomized controlled trials can help lessen confounding factors and biases in case–control studies. Increasing the quality of studies through patient selection, randomization, and timing, along with adherence to rigorous methodological standards, will further enhance reliability and reduce bias. In the present review, we prioritized studies that compared both [68Ga] FAPI PET/CT and [18F] FDG PET/CT under similar conditions and sample sizes. However, this approach ensured consistency, it also reduced the number of eligible studies. Future investigations could independently evaluate [68Ga] FAPI PET/CT and [18F] FDG PET/CT in larger, standalone studies to provide more comprehensive insights into their diagnostic capabilities.

Conclusions

[68Ga] FAPI- 46 PET/CT has recently been considered a superior diagnostic agent to [18F] FDG PET/CT for different cancers, due to its higher sensitivity and specificity than [18F] FDG PET/CT. It also improves primary and metastatic tumor detection with a higher TBR, leading to accurate distinguishing of tumors from surrounding tissues. Additionally, [68Ga] FAPI- 46 PET/CT exhibits a great capability to identify malignancies associated with lower uptake in normal tissues, such as the liver and muscle. In clinical practice, these advantages lead to a decrease in false-negative and false-positive results and thus a more dependable diagnosis and treatment planning. Further, the acquisition of imaging data shortly after administration without any requirement for patient fasting, which is crucial for [18F] FDG, can streamline the imaging process. Therefore, these advantages suggest that [68Ga] FAPI- 46 could be positioned as a promising next-generation imaging agent in diagnostic strategies. However, future studies are needed to more validation of its effectiveness and potential in clinical applications. Additionally, limitations, such as small sample sizes, limited clinical data for different cancer types, and variability in performance based on cancer type and patient characteristics could impact its ability to distinguish certain tumors from surrounding tissues. Furthermore, the availability, accessibility, and cost-effectiveness of [68Ga] FAPI- 46 warrant further investigation before its wide implementation in clinical practice.

Abbreviations

CT	Computed tomography
PET	Positron emission tomography
FAP and FAPI	Fibroblast activation protein (FAP) inhibitor (FAPI)
CAF	Cancer-associated fibroblasts
MRI	Magnetic resonance imaging
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
FDG	Fluorodeoxyglucose (FDG)
SUV	Standardized uptake values
TBR	Tumor-to-breast volume ratio
TP, TN	True positive and negative
FP, FN	False positive and negative
SROC	Summary receiver operating characteristic
AUC	Area under the curve
QUADAS	The Quality Assessment of Diagnostic Accuracy Studies
CI	Confidence intervals
LR	Likelihood ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-025-02835-x.

Additional file 1: Table S1: Search strategy.

Acknowledgements
None.

Authors' contributions
S. A. and A. M. conducted the systematic review and wrote the manuscript. M. S. (Sadeghi) did the meta-analysis, M. D., S. KH., M. T., and Z. P rechecked the process and revised the text. M. S (Sahebi) helped conduct a part of analysis. A. M as a supervisor finally rechecked the findings and the text. All authors reviewed, discussed, revised manuscript critically for important intellectual content, and approved the manuscript.

Funding
We would like to acknowledge that this work received no funding from any organization or entity.

Data Availability
The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study did not involve human participants or animals, and therefore ethical approval was not required.

Competing interests
The authors declare that they have no conflicts of interest.

Author details
[1]Department of Medical Physics, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. [2]Department of Epidemiology, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran. [3]Department of Radiology Technology, School of Paramedical Sciences, Mashhad University of Medical Sciences, Mashhad, Iran. [4]Fintech in Medicine Research Center, Iran University of Medical Science, Tehran, Iran. [5]Nuclear Medicine and Molecular Imaging Department, Imam Reza International University, Razavi Hospital, Mashhad, Iran. [6]Medical Physics Research Center, Mashhad

University of Medical Sciences, Mashhad, Iran. [7]Department of Radiation Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA.

Received: 25 December 2024 Accepted: 27 March 2025
Published online: 10 May 2025

References

1. Quasar SR, Sharma R, Mittal A, Sharma M, Agarwal D, de La Torre DI. Ensemble methods for computed tomography scan images to improve lung cancer detection and classification. Multimedia Tools and Applications. 2024;83(17):52867–97.
2. Lanjewar MG, Panchbhai KG, Charanarur P. Lung cancer detection from CT scans using modified DenseNet with feature selection methods and ML classifiers. Expert Syst Appl. 2023;224:119961.
3. Lee JE, Park K-S, Kim Y-H, Song H-C, Park B, Jeong YJ. Lung cancer staging using chest CT and FDG PET/CT free-text reports: comparison among three ChatGPT large-language models and six human readers of varying experience. Am J Roentgenol. 2024;223(6):e2431696.
4. Adam R, Dell'Aquila K, Hodges L, Maldjian T, Duong TQ. Deep learning applications to breast cancer detection by magnetic resonance imaging: a literature review. Breast Cancer Res. 2023;25(1):87.
5. Singnurkar A, Poon R, Metser U. Head-to-head comparison of the diagnostic performance of FDG PET/CT and FDG PET/MRI in patients with cancer: a systematic review and meta-analysis. Am J Roentgenol. 2024;223(3):e2431519.
6. Xu W, Cai J, Peng T, Meng T, Pang Y, Sun L, et al. Fibroblast activation protein–targeted PET/CT with 18F-fibroblast activation protein inhibitor-74 for evaluation of gastrointestinal cancer: comparison with 18F-FDG PET/CT. J Nucl Med. 2024;65(1):40–51.
7. Sutherland DE, Azad AA, Murphy DG, Eapen RS, Kostos L, Hofman MS, editors. Role of FDG PET/CT in management of patients with prostate cancer. Seminars in nuclear medicine; 2024: Elsevier.
8. Wei Y, Ma L, Li P, Lu J, Ren J, Yan S, et al. FAPI Compared with FDG PET/CT for Diagnosis of Primary and Metastatic Lung Cancer. Radiology. 2023;308(2):e222785.
9. Tan H, Sui X, Yin H, Yu H, Gu Y, Chen S, et al. Total-body PET/CT using half-dose FDG and compared with conventional PET/CT using full-dose FDG in lung cancer. Eur J Nucl Med Mol Imaging. 2021;48:1966–75.
10. Parihar AS, Dehdashti F, Wahl RL. FDG PET/CT–based response assessment in malignancies. Radiographics. 2023;43(4):e220122.
11. Nourbakhsh S, Salehi Y, Farzanehfar S, Ghaletaki R, Kashi MB, Abbasi M. FAPI PET/CT provides higher uptake and better target to back ground in recurrent and metastatic tumors of patients with Iodine refractory papillary thyroid cancer compared with FDG PET CT. NuklearmedizinNuclearMedicine. 2024. https://doi.org/10.1055/a-2185-7746.
12. Liu L, Zhong J, Zhang Z, Ye X, Wang X, Liu S, et al. Preclinical study and first-in-human imaging of [18F] FAP-2286, and comparison with 2-[18F] FDG PET/CT in various cancer patients. Eur J Nucl Med Mol Imaging. 2024;51(7):2012–22.
13. Katal S, Eibschutz LS, Saboury B, Gholamrezanezhad A, Alavi A. Advantages and applications of total-body PET scanning. Diagnostics. 2022;12(2):426.
14. Mehranian A, Wollenweber SD, Walker MD, Bradley KM, Fielding PA, Su K-H, et al. Image enhancement of whole-body oncology [18F]-FDG PET scans using deep neural networks to reduce noise. Eur J Nucl Med Mol Imaging. 2022;49(2):539–49.
15. Liu J, Cundy TP, Woon DT, Lawrentschuk N. A systematic review on artificial intelligence evaluating metastatic prostatic cancer and lymph nodes on psma pet scans. Cancers. 2024;16(3):486.
16. Mohseninia N, Zamani-Siahkali N, Harsini S, Divband G, Pirich C, Beheshti M. Bone metastasis in prostate cancer: bone scan versus PET imaging. Seminars in Nuclear Medicine. 2024;54(1):97–118.
17. Gui J, Li M, Xu J, Zhang X, Mei H, Lan X. [18F] FDG PET/CT for prognosis and toxicity prediction of diffuse large B-cell lymphoma patients with chimeric antigen receptor T-cell therapy. Eur J Nucl Med Mol Imaging. 2024;51(8):2308–19.
18. Gerke O, Naghavi-Behzad M, Nygaard ST, Sigaroudi VR, Vogsen M, Vach W, et al. Diagnosing bone metastases in breast cancer: a systematic review and network meta-analysis on diagnostic test accuracy studies of 2-[18F] FDG-PET/CT, 18F-NaF-PET/CT, MRI, contrast-enhanced CT, and bone scintigraphy. Semin Nuclear Med. 2025;55(1):137–51.
19. Ferrara D, Abenavoli EM, Beyer T, Gruenert S, Hacker M, Hesse S, et al. Detection of cancer-associated cachexia in lung cancer patients using whole-body [18F] FDG-PET/CT imaging: A multi-centre study. J Cachexia Sarcopenia Muscle. 2024;15(6):2375–86.
20. Yoshikawa T, Endo K, Moriyama-Kita M, Ueno T, Nakanishi Y, Dochi H, et al. Association of 18F-fluorodeoxyglucose uptake with the expression of metabolism-related molecules in papillary thyroid cancer. Auris Nasus Larynx. 2024;51(4):696–702.
21. Elhaie M, Koozari A, Abedi I, Monsef A. Advancing Oncology through Imaging: Evaluating FDG-PET's Role in Cancer Diagnosis and Staging. Frontiers in Biomedical Technologies. 2024;11(4):662–9.
22. Elsoudy NM, Anwar M, Amer HH, Yassien HM, Abdelazeez LM. Effect of some physiological and technical factors on Effective Dose Estimation of Patients Administered with 18F-FDG in PET/CT. Radiat Phys Chem. 2025;229:112438.
23. Garcia J, Kauak M, Compte A, Bassa P, Llinares E, Valls E, et al. Detection of internal mammary chain infiltration in breast cancer patients by [18F] FDG PET/MRI. Therapy implications. Revista Española de Medicina Nuclear e Imagen Molecular (English Edition). 2024;43(2):73–8.
24. Luo Z-H, Luo X-Y, Qi W-L, Liu Q. 18F-FDG PET/CT imaging in pulmonary sarcomatoid carcinoma. Front Oncol. 2024;14:1334156.
25. Mirshahvalad SA, Eisazadeh R, Shahbazi-Akbari M, Pirich C, Beheshti M. Application of Artificial intelligence in oncologic molecular PET-imaging: a narrative review on beyond [18F] F-FDG tracers-part I. PSMA, choline, and DOTA radiotracers. Semin Nuclear Med. 2024;54(1):171–80.
26. Guo X, Zhou N, Liu J, Ding J, Liu T, Song G, et al. Comparison of an Affibody-based molecular probe and 18F-FDG for detecting HER2-positive breast cancer at PET/CT. Radiology. 2024;311(3):e232209.
27. Willemse JR, Lambregts DM, Balduzzi S, Schats W, Snaebjornsson P, Marchetti S, et al. Identifying the primary tumour in patients with cancer of unknown primary (CUP) using [18F] FDG PET/CT: a systematic review and individual patient data meta-analysis. Eur J Nucl Med Mol Imaging. 2024;52(1):225–36.
28. Christou CN, Sandström K, Regula N, Ehrsson YT, Johansson H, Sörensen J, et al. Prognostic value of bone marrow and tumor 18F-FDG uptake on PET/CT in patients with oropharyngeal cancer and the interplay between inflammation and FDG uptake. Head Neck. 2024;46(10):2422–31.
29. Donnelly R, McDermott M, McManus G, Franciosi AN, Keane MP, McGrath EE, et al. Meta-analysis of [18F] FDG-PET/CT in pulmonary sarcoidosis. European Radiology. 2024:1–11.
30. Hicks RJ, Ware RE, Callahan J. Total-body PET/CT: pros and cons. Semin Nuclear Med. 2025;55(1):11–20.
31. Ng SJ, Lau HC, Raynor W, Werner T, Saboury B, Revheim M-E, et al. Diagnosis and evaluation of cardiac sarcoidosis with FDG PET/CT and PET/MR. Soc Nuclear Med. 2022;63(2):2641.
32. Manda D, Thakral P, Sen I, Das SS, Virupakshappa C, Malik D. Incremental Value of 18F-FDG–Labeled Leukocytes PET/CT Over 18F-FDG PET/CT Scan in the Detection of Occult Infection. Clin Nucl Med. 2022;47(9):e574–81.
33. Huang R, Pu Y, Huang S, Yang C, Yang F, Pu Y, et al. FAPI-PET/CT in Cancer Imaging: A Potential Novel Molecule of the Century. Front Oncol. 2022;12:854658.
34. Novruzov F, Mehdi E, Orucova N, Aliyeva G, Shukurov R, Dadashov Z, et al. Head to head comparison of 68Ga-FAPI-46 PET/CT and 18-FDG PET/CT in breast carcinoma staging: a clinical trial update from Azerbaijan. Soc Nuclear Med. 2022;63(2):2372.
35. Guglielmo P, Alongi P, Baratto L, Abenavoli E, Buschiazzo A, Celesti G, et al. Head-to-head comparison of FDG and radiolabeled FAPI PET: a systematic review of the literature. Life. 2023;13(9):1821.
36. Wegen S, Roth KS, Weindler J, Claus K, Linde P, Trommer M, et al. First clinical experience with [68Ga] Ga-FAPI-46-PET/CT versus [18F] F-FDG PET/CT for nodal staging in cervical cancer. Clin Nucl Med. 2023;48(2):150–5.
37. Qin C, Shao F, Gai Y, Liu Q, Ruan W, Liu F, et al. 68Ga-DOTA-FAPI-04 PET/MR in the evaluation of gastric carcinomas: comparison with 18F-FDG PET/CT. J Nucl Med. 2022;63(1):81–8.
38. Hathi DK, Jones EF. 68Ga FAPI PET/CT: tracer uptake in 28 different kinds of cancer. Radiology: Imaging Cancer. 2019;1(1):e194003.
39. Novruzov F, AANSONAIMMVFGFME. Comparison [68Ga]FAPI-46 PET/CT and [131I] SPECT/CT findings after ablation therapy with high-activity

131-I therapy of metastatic papillary thyroid cancer patients: Two case reports. Eur J Nuclear Med Mol Imaging. 2021;48:S100–1.
40. Chen H, Pang Y, Wu J, Zhao L, Hao B, Wu J, et al. Comparison of [68 Ga] Ga-DOTA-FAPI-04 and [18 F] FDG PET/CT for the diagnosis of primary and metastatic lesions in patients with various types of cancer. Eur J Nucl Med Mol Imaging. 2020;47:1820–32.
41. Kratochwil C, Flechsig P, Lindner T, Abderrahim L, Altmann A, Mier W, et al. 68Ga-FAPI PET/CT: tracer uptake in 28 different kinds of cancer. J Nucl Med. 2019;60(6):801–5.
42. Meyer C, Dahlbom M, Lindner T, Vauclin S, Mona C, Slavik R, et al. Radiation dosimetry and biodistribution of 68Ga-FAPI-46 PET imaging in cancer patients. J Nucl Med. 2020;61(8):1171–7.
43. Watanabe M, Fendler WP, Grafe H, Hirmas N, Hamacher R, Lanzafame H, et al. Prognostic Implications of 68Ga-FAPI-46 PET/CT–Derived Parameters on Overall Survival in Various Types of Solid Tumors. J Nucl Med. 2024;65(7):1027–34.
44. Zhang J, Xiong J, Wang M, Wu B, Zhang C. Comparison of the diagnostic value of 68Ga-FAPI and 18F-FDG PET/CT in breast cancer: a systematic review. Clinical and Translational Imaging. 2024;12(6):787–98.
45. Jiang Y, Wen B, Li C, Tian Y, Xiao Z, Xu K, et al. The performance of 68Ga-FAPI-04 PET/CT in head and neck squamous cell carcinoma: a prospective comparison with 18F-FDG PET/CT. Eur J Nucl Med Mol Imaging. 2023;50(7):2114–26.
46. Kuyumcu S, Isik EG, Şen C, Has-Şimsek D, Başaran B, Özkan ZG, et al. [68Ga] Ga-FAPI04 outperforms [18F] FDG PET/CT for detecting nodal metastasis of head and neck squamous cell carcinoma: a single-center experience. Cancer Biotherapy and Radiopharmaceuticals. 2024;40(2):122–9.
47. Rizzo A, Miceli A, Racca M, Bauckneht M, Morbelli S, Albano D, et al. Diagnostic accuracy of [68Ga] Ga labeled fibroblast-activation protein inhibitors in detecting head and neck cancer lesions using positron emission tomography: A systematic review and a meta-analysis. Pharmaceuticals. 2023;16(12):1664.
48. Kömek H, Can C, Kaplan İ, Gündoğan C, Kepenek F, Karaoglan H, et al. Comparison of [68 Ga] Ga-DOTA-FAPI-04 PET/CT and [18F] FDG PET/CT in colorectal cancer. Eur J Nucl Med Mol Imaging. 2022;49(11):3898–909.
49. Pang Y, Zhao L, Luo Z, Hao B, Wu H, Lin Q, et al. Comparison of 68Ga-FAPI and 18F-FDG Uptake in Gastric, Duodenal, and Colorectal Cancers. Radiology. 2021;298(2):393–402.
50. Pang Y, Zhao L, Shang Q, Meng T, Zhao L, Feng L, et al. Positron emission tomography and computed tomography with [68 Ga] Ga-fibroblast activation protein inhibitors improves tumor detection and staging in patients with pancreatic cancer. Eur J Nucl Med Mol Imaging. 2022;49(4):1322–37. https://doi.org/10.1007/s00259-021-05576-w. Epub 2021 Oct 15.
51. Wang L, Tang G, Hu K, Liu X, Zhou W, Li H, et al. Comparison of 68Ga-FAPI and 18F-FDG PET/CT in the evaluation of advanced lung cancer. Radiology. 2022;303(1):191–9.
52. Gu B, Xu X, Zhang J, Ou X, Xia Z, Guan Q, et al. The added value of 68Ga-FAPI PET/CT in patients with head and neck cancer of unknown primary with 18F-FDG–negative findings. J Nucl Med. 2022;63(6):875–81.
53. Guo W, Pang Y, Yao L, Zhao L, Fan C, Ke J, et al. Imaging fibroblast activation protein in liver cancer: a single-center post hoc retrospective analysis to compare [68 Ga] Ga-FAPI-04 PET/CT versus MRI and [18 F]-FDG PET/CT. Eur J Nucl Med Mol Imaging. 2021;48:1604–17.
54. Zhao L, Pang Y, Luo Z, Fu K, Yang T, Zhao L, et al. Role of [68 Ga] Ga-DOTA-FAPI-04 PET/CT in the evaluation of peritoneal carcinomatosis and comparison with [18 F]-FDG PET/CT. Eur J Nucl Med Mol Imaging. 2021;48:1944–55.
55. Guo W, Chen H. 68Ga FAPI PET/CT imaging in peritoneal carcinomatosis. Radiology. 2020;297(3):521.
56. Novruzov F, MEDZMMVFTTGFGFAJ. [68ga]fapi-46 [18f]fdg and [68ga] psma-11 pet/ ct findings in advance stage castration resistant metastatic prostate carcinoma treated with tandem radionuclide [225ac]/[177lu] psma-617: two case reports. European journal of nuclear medicine and molecular imaging. 2021;48:S571–2.
57. Unterrainer L, M LSELCJGFJBVNANLHABLTAB. Feasibility of [68Ga]Ga-FAPI-46 PET/CT for detection of nodal and hematogenous spread in high-grade urothelial carcinoma. European journal of nuclear medicine and molecular imaging. 2022;49:3571–80.
58. Bentestuen M, Al-Obaydi N, Zacho HD. FAPI-avid nonmalignant PET/CT findings: an expedited systematic review. Semin Nuclear Med. 2023;53(5):694–705.
59. Elboga U, Sahin E, Cayirli YB, Okuyan M, Aktas G, Haydaroglu Sahin H, et al. Comparison of [68Ga]-FAPI PET/CT and [18F]-FDG PET/CT in multiple myeloma: clinical experience. Tomography. 2022;8(1):293–302.
60. Hu X, Li X, Wang P, Cai J. The Role of FAPI PET Imaging in Pancreatic Cancer: A Meta-analysis Compared with 18F-FDG PET. Acad Radiol. 2025;32(1):191–200.
61. Gao C, Liu H, Zhou L, Huang W, Liu X. Head to head comparison of 68 Ga-FAPI PET/CT with 18 F-FDG PET/CT in primary and metastatic lesions of gastric tumor: A systematic review and meta-analysis. Hell J Nuclear Med. 2024;27(1):35–45.
62. Liu X, Liu H, Gao C, Zeng W. Comparison of 68Ga-FAPI and 18F-FDG PET/CT for the diagnosis of primary and metastatic lesions in abdominal and pelvic malignancies: A systematic review and meta-analysis. Front Oncol. 2023;13:1093861.
63. Gege Z, Xueju W, Bin J. Head-to-head comparison of 68Ga-FAPI PET/CT and FDG PET/CT for the detection of peritoneal metastases: systematic review and meta-analysis. Am J Roentgenol. 2023;220(4):490–8.
64. Zhuang Z, Zhang Y, Yang X, Deng X, Wang Z. Head-to-head comparison of the diagnostic performance between 68Ga-FAPI-04 PET/CT and 18F-FDG PET/CT in colorectal cancer: a systematic review and meta-analysis. Abdom Radiol. 2024;49(9):3166–74.
65. Yang Q, Huang D, Wu J, Zhong H, Han Y, Jiang H, et al. Performance of [18F] FDG PET/CT versus FAPI PET/CT for lung cancer assessment: a systematic review and meta-analysis. Eur Radiol. 2024;34(2):1077–85.
66. Ouyang J, Ding P, Zhang R, Lu Y. Head-to-head comparison of 68Ga-FAPI-04 PET/CT and 18F-FDG PET/CT in the evaluation of primary digestive system cancer: a systematic review and meta-analysis. Front Oncol. 2023;13:1202505.
67. Jiao M, Mingsong T, Hao J, Chunyin Z. Diagnostic value of 18F-FDG PET/CT and 68Ga-FAPI PET/CT in primary liver cancer: A systematic review and meta-analysis. Hellenic Journal of Nuclear Medicine. 2023;26(2):123–31.
68. Watanabe M, Fendler WP, Grafe H, Hirmas N, Hamacher R, Lanzafame H, et al. Head-to-head comparison of 68 Ga-FAPI-46 PET/CT, 18F-FDG PET/CT, and contrast-enhanced CT for the detection of various tumors. Ann Nucl Med. 2025;39(3):255–65.
69. McInnes MD, Moher D, Thombs BD, McGrath TA, Bossuyt PM, Clifford T, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. JAMA. 2018;319(4):388–96.
70. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529–36.
71. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods. 2006;11(2):193.
72. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58.
73. Kessler L, FJHNBSDUZFNMCMMAULSMPLESH-UFWP. 68Ga-FAPI as a Diagnostic Tool in Sarcoma: Data from the 68Ga-FAPI PET Prospective Observational Trial. Journal of nuclear medicine : official publication Society of Nuclear Medicine. 2022;63:89–95.
74. Promteangtrong Chetsadaporn SDJAKAKPYSBNCC. Head-to-Head Comparison of 68Ga-FAPI-46 and 18F-FDG PET/CT for Evaluation of Head and Neck Squamous Cell Carcinoma: A Single-Center Exploratory Study. Journal of nuclear medicine : official publication Society of Nuclear Medicine. 2022;63:1155–61.
75. Roth K, S VCAvHLWSSKFTMSDAKC. Dual-tracer PET/CT protocol with [18F]-FDG and [68Ga]Ga-FAPI-46 for cancer imaging: a proof of concept. Journal of nuclear medicine : official publication Society of Nuclear Medicine. 2022;63:1683–6.
76. Siripongsatian D, PCKAKPBNCCJACC. Comparisons of quantitative parameters of Ga-68-labelled fibroblast activating protein inhibitor (FAPI) PET/CT and [18F]F-FDG PET/CT in patients with liver malignancies. Mol Imaging Biol. 2022;24:818–29.
77. Wegen S, vHLLPCKA-BDBCSSJSKFTRKSKJ. Head-to-Head Comparison of [68 Ga]Ga-FAPI-46-PET/CT and [18F]F-FDG-PET/CT for Radiotherapy

Planning in Head and Neck Cancer. Molecular imaging and biology. 2022;24:986–94.
78. Guo W, Fu H, Pang Y, Sun L, Wu H, Chen H. 68Ga-Labeled Fibroblast Activation Protein Inhibitor PET/CT for the Early and Late Prediction of Pathologic Response to Neoadjuvant Chemotherapy in Breast Cancer Patients: A Prospective Study. J Nucl Med, 2023;64(12):1899–905. https://doi.org/10.2967/jnumed.123.266079.
79. Pabst K, M T-AMCPFYBSSKBTSBMMASRNM. Superior tumor detection for 68Ga-FAPI-46 versus 18F-FDG PET/CT and conventional CT in patients with cholangiocarcinoma. J Nuclear Med. 2023;64:1049–55.
80. Wegen S, RKSWJCKLPTMA-BDVHLBCS-MBSK. First clinical experience with [68Ga]Ga-FAPI-46-PET/CT versus [18F]F-FDG PET/CT for nodal staging in cervical cancer. Clinical nuclear medicine. 2023;48:150–5.
81. Kang Y, K NKJPJKNLYSCHKYT. Preoperative evaluation of mediastinal lymph nodes in non-small cell lung cancer using [68Ga]FAPI-46 PET/CT: a prospective pilot study. Eur J Nuclear Med Mol Imaging. 2024;51:2409–19.
82. Sahin E, Kus T, Aytekin A, Uzun E, Elboga U, Yilmaz L, et al. 68Ga-FAPI PET/CT as an Alternative to 18F-FDG PET/CT in the Imaging of Invasive Lobular Breast Carcinoma. J Nucl Med. 2024;65(4):512–9.
83. Singh P, Singhal T, Parida GK, Rahman A, Agrawal K. Diagnostic performance of FAPI PET/CT vs. 18 F-FDG PET/CT in evaluation of liver tumors: a systematic review and meta-analysis. Mol Imaging Radionuclide Therapy. 2024;33(2):77–89.
84. Radmehr K, Farzanehfar S, Abbasi M, Salehi Y, Karamzade Ziarati N, Emami-Ardekani A, et al. Comparative diagnostic performance of [68Ga] Ga-FAPI-46 and [18F] FDG PET/CT imaging for the detection of active lesions and disease stage evaluation in breast cancer patients. Asia Oceania Journal of Nuclear Medicine and Biology. 2024;13(1):1.
85. Kline B, Yadav S, Seo Y, Ippisch RC, Castillo J, Aggarwal RR, et al. 68Ga-FAP-2286 PET of Solid Tumors: Biodistribution, Dosimetry, and Comparison with 18F-FDG. J Nucl Med. 2024;65(6):938–43.
86. Pabst KM, Trajkovic-Arsic M, Cheung PF, Ballke S, Steiger K, Bartel T, et al. Superior tumor detection for 68Ga-FAPI-46 versus 18F-FDG PET/CT and conventional CT in patients with cholangiocarcinoma. J Nucl Med. 2023;64(7):1049–55.
87. Novruzov F, MEMHSRDZVMBMAGFKVFAJ. The added value of [68Ga] Ga-FAPI-46 to 2-[18F]FDG in differential diagnosis of Malignant Melanoma. European journal of nuclear medicine and molecular imaging. 2022;49:S12.
88. Wegen S, van Heek L, Linde P, Claus K, Akuamoa-Boateng D, Baues C, et al. Head-to-head comparison of [68 Ga] Ga-FAPI-46-PET/CT and [18F] F-FDG-PET/CT for radiotherapy planning in head and neck cancer. Mol Imag Biol. 2022;24(6):986–94.
89. Kaghazchi F, Divband G, Amini H, Adinehpour Z, Aghdam RA. 68Ga-FAPI-46 and 18F-FDG in advanced metastatic pancreatic cancer. Clin Nucl Med. 2022;47(10):e666–9.
90. Can C, Kepenek F, Kömek H, Gündoğan C, Kaplan I, Taşdemir B, et al. Comparison of 18F-FDG PET/CT and 68Ga-FAPI-04 PET/CT in patients with non-small cell lung cancer. Nucl Med Commun. 2022;43(10):1084–91.
91. Ruan D, Sun J, Han C, Cai J, Yu L, Zhao L, et al. 68Ga-FAPI-46 PET/CT in the evaluation of gliomas: comparison with 18F-FDG PET/CT and contrast-enhanced MRI. Theranostics. 2024;14(18):6935.
92. Oster C, Kessler L, Blau T, Keyvani K, Pabst KM, Fendler WP, et al. The Role of Fibroblast Activation Protein in Glioblastoma and Gliosarcoma: A Comparison of Tissue, 68Ga-FAPI-46 PET Data, and Survival Data. J Nucl Med. 2024;65(8):1217–23.
93. Pabst KM, Mei R, Lückerath K, Hadaschik BA, Kesch C, Rawitzer J, et al. Detection of tumour heterogeneity in patients with advanced, metastatic castration-resistant prostate cancer on [68Ga]Ga-/[18F]F-PSMA-11/-1007, [68Ga]Ga-FAPI-46 and 2-[18F]FDG PET/CT: a pilot study. Eur J Nucl Med Mol Imaging. 2024;52(1):342–53. https://doi.org/10.1007/s00259-024-06891-8. Epub 2024 Aug 29.
94. Umachanger JK, Zacho HD, Sylvest C, Frandsen AP, Bentestuen M. Predicting malignancy in adnexal tumors with FAPI PET/CT and FDG PET/CT: a case report on a borderline ovarian tumor. Clin Nucl Med. 2025;50(2):e124–6.
95. Wang L, Pan X, Ye S, Huang Y, Wang M, Chen L, et al. [18F] F-FAPI-42 PET dynamic imaging characteristics and multiparametric quantification of lung cancer: an exploratory study using uEXPLORER PET/CT. Eur J Nucl Med Mol Imaging. 2025;52(5):1685–94. https://doi.org/10.1007/s00259-024-07064-3. Epub 2025 Jan 6.
96. Guglielmo P, Alongi P, Baratto L, Conte M, Abenavoli EM, Buschiazzo A, et al. FAPi-based agents in thyroid cancer: a new step towards diagnosis and therapy? A systematic review of the literature. Cancers. 2024;16(4):839.
97. Li T, Zhang J, Yan Y, Tan M, Chen Y. Applications of FAPI PET/CT in the diagnosis and treatment of breast and the most common gynecologic malignancies: a literature review. Front Oncol. 2024;14:1358070.

Publisher's Note