REVIEW

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Performance of [^{68}Ga]Ga-FAPI PET in Breast, Ovarian, and Cervical Cancers: A Systematic Review and Meta-Analysis

Madina Gabdullina[1,2]*, Akmaral Ainakulova[1,3], Umut Elboga[4], Indira Karibayeva[5], Galymzhan Alisherov[1], Zhanar Zhakenova[1], Jandos Amankulov[1,3], Zhamilya Zholdybay[1]

Abstract

Objective: This meta-analysis aims to evaluate the diagnostic efficacy of [^{68}Ga]Ga-FAPI PET imaging in breast, ovarian, and cervical cancers by conducting a systematic review of the existing literature. **Methods:** A systematic review of PubMed, Web of Science, Scopus, and Google Scholar databases, following by a meta-analysis of the included studies, was performed using a random-effects statistical model. **Result:** Ten eligible studies that described the effectiveness of [^{68}Ga]Ga-FAPI PET imaging in breast, ovarian, and cervical cancers were included in this review. The total number of participants was 253 females. Aggregated data from nine studies indicate a remarkably high diagnostic odds ratio (DOR) of 48.69 (95% CI: [16.94–139.96]) for detecting primary tumors, and a DOR of 207.50 (95% CI: [46.18–932.34]) from seven studies for detecting lymph node metastasis. [^{68}Ga]Ga-FAPI PET demonstrated high diagnostic accuracy in identifying both primary lesions and metastatic lymph nodes in breast, ovarian, and cervical cancers. **Conclusion:** [^{68}Ga]Ga-FAPI PET imaging could function as a supplementary technique to [^{18}F]F-FDG PET imaging modalities, offering a more comprehensive evaluation for cancer staging, assessment of treatment response, and guidance in radiation therapy planning.

Keywords: Breast cancer- Ovarian cancer- Cervical cancer- [^{68}Ga]Ga-FAPI-04 PET- [^{68}Ga]Ga-FAPI-46 PET

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Introduction

Positron emission tomography (PET) is a noninvasive imaging method using radiopharmaceuticals. The combination of PET and computed tomography (CT) or magnetic resonance imaging (MRI) provides anatomical, metabolic, and molecular information on malignant tumors, which is useful for staging, restaging, therapy planning, prognosis and therapy efficacy assessment [1-4]. According to the National Comprehensive Cancer Network (NCCN) recommendations whole-body PET becomes one of the standard imaging modalities for various cancers [5-7].

Nowadays, the most widely used radiopharmaceutical is 2-deoxy-2[^{18}F]fluoro-D-glucose ([^{18}F]F-FDG). However, [^{18}F]F-FDG lacks sensitivity and specificity (with values of 48-96% and 73-100%, respectively) due to its high physiological accumulation in organs and its low avidity for certain histological cancer subtypes [8-11].

The identification of fibroblast activation protein (FAP) in 2018 was followed by an increased interest in FAP-targeted radiolabeled inhibitors (FAPIs) [12-17]. Gallium-68 [^{68}Ga]-labeled FAPI ([^{68}Ga]Ga-FAPI) is one of the most sensitive and specific markers of FAP. The first guideline on FAP PET, published in January 2025, indicates potential clinical applications for tumors with both high and low concentrations of cancer associated fibroblasts (CAFs) as well as tumors in which FAP is expressed on both the stroma and the tumor cells. Another potential application is presented by tumors in which FDG PET is limited due to its high physiological uptake or low FDG avidity. Consequently, the indications include gastrointestinal cancers, head and neck cancers, and thyroid, lung, peritoneal, ovarian and breast cancers [18]. Published meta-analyses have demonstrated that [^{68}Ga]Ga-FAPI PET/CT has high diagnostic accuracy for primary staging (98%) and restaging (91%) of abdominal cancers, as well as for detecting peritoneal metastases (98.2%) and lung metastases (99%) [19-21].

Some authors have reported that FAP is of particular

*[1]Department of Visual Diagnostics, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan. [2]Faculty of Medicine and Healthcare, Al-Farabi Kazakh National University, Almaty, Kazakhstan. [3]Department of Oncology and Radiology, Kazakh Institute of Oncology and Radiology, Almaty, Kazakhstan. [4]Department of Nuclear Medicine, Faculty of Medicine, Gaziantep University, Gaziantep, Turkiye. [5]Department of Health Policy and Community Health, Jiann-Ping Hsu College of Public Health, Georgia Southern University, Statesboro, GA, USA. *For Correspondence: gabdullina.m@kaznmu.kz*

interest in the imaging of hormone-dependent tumors, such as breast, ovarian and endometrial cancers [19, 20]. In 2020, breast cancer was the most diagnosed cancer among women worldwide, causing 2.3 million new cases and nearly 700,000 deaths (6.9% of all cancer deaths) [21]. Breast cancer primarily affects women exerting a significant burden on healthcare systems due to its high incidence and substantial morbidity and mortality rates among women. Ovarian (1.6%), cervical (3.1%), and endometrial (2.2%) cancers also rank among the top ten most common cancers in women by incidence [21]. Although these tumor types differ in their molecular biology and clinical progression, they share several key diagnostic hurdles, such as the accurate detection of primary tumors and the reliable assessment of lymph node involvement. Traditional imaging modalities, particularly [^{18}F]F-FDG PET, underperform in these settings due to suboptimal sensitivity in certain breast cancer subtypes, such as invasive lobular carcinoma [8, 9] and high physiological accumulation in the liver and intestines, which leads to a low tumor-to-background ratio (TBR) and reduced sensitivity for detecting lymph node metastases in ovarian and cervical cancers [22-25].

The aim of this study was to evaluate the effectiveness of [^{68}Ga]Ga-FAPI PET imaging in visualizing breast, ovarian, and cervical cancers.

Materials and Methods

The study protocol has been registered with the PROSPERO International Prospective Register of Systematic Reviews (ID: CRD42024530820, https://www.crd.york.ac.uk/PROSPERO/view/CRD42024530820).

The search was conducted in four major electronic literature databases: PubMed, Scopus, Google Scholar, and Web of Science (latest search: February 10, 2024). The timeframe was limited to 2018 through 2024, as FAPI-based radiotracers were first described in 2018. The search strategy included the keywords "breast cancer"; "ovarian cancer"; "cervical cancer"; "uterine cancer"; "endometrial cancer"; "gynecological malignancies"; "[^{68}Ga]Ga-FAPI PET/CT"; "[^{68}Ga]Ga-FAPI PET/MRI"; "positron emission tomography"; "PET scan"; "fibroblast activation protein inhibitor"; "FAP"; and "Gallium-68". The operators "AND", "OR" and "NOT" were used to narrow or broaden the search. The search strategy, including Medical Subject Headings (MeSH) and keywords, was performed using PubMed Advanced.

Eligibility criteria

Methodologically, the literature screening and synthesis followed the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [26]. The inclusion criteria were as follows: 1) cohort studies or randomized clinical trials; 2) female patients with histologically confirmed breast cancer, ovarian or cervical cancers who were examined using [^{68}Ga]Ga-FAPI PET; 3) reported rates of sensitivity and specificity; and 4) studies published in English. The exclusion criteria were as follows: 1) lack of sensitivity and specificity rates; 2) unsuitable patient population (cancer of localizations other than breast, ovaries or cervix); 3) unsuitable radiotracer (other than [^{68}Ga]Ga-FAPI); 4) studies describing only theranostic applications; 5) studies not in English; 6) articles not conducting gold-standard for diagnosis; 7) review articles and case reports; and 8) cases where the full text was not available.

Study selection and data extraction

The first (MG) and the second author (AA) conducted the database search independently following the inclusion and exclusion criteria, as suggested by the PRISMA Guidelines [26]. After removing duplicates, two authors (MG and AA) independently performed manual screening by title and abstract (Figure 1). Disagreements were resolved by the involvement of an additional author (IK). Next, full-text papers were assessed for eligibility with exclusions made according to the criteria. The extracted data included the first author's last name, year of publication, country, study type, radiotracer type, cancer type, imaging techniques, number of patients, number of lesions, age range, lesion location (primary or lymph node metastasis), true positive (TP), true negative (TN), false positive (FP) and false negative (FN) rates.

Risk of Bias Assessment and Quality Assessment

The methodological quality of the studies included was assessed using the Critical Appraisal Skills Programme (CASP) checklist for diagnostic test studies, which consists of 12 questions addressing the validity of the results, outcome and applicability of the results [27]. An affirmative "yes" indicated comprehensive reporting (score of 1), a "no" was used for absent reports (score of 0) and a "can't tell" was used for incomplete information (score of 0.5). All studies scored 7 and above on the CASP scale (Table 1). Two researchers conducted the critical appraisal, and any disagreements were resolved through discussion.

Statistical analysis

Descriptive statistics were used to present the systematic review. All tables are organized chronologically (earlier publications first) and alphabetically by the first author's last name. A paired forest plot analysis was generated to present the sensitivity and specificity. Following the established recommendations for conducting meta-analyses of diagnostic test accuracy, the pooling of raw sensitivity and specificity values is not advised. Instead, meta-analytic summary measures such as summary sensitivity and specificity, diagnostic odds ratio (DOR), and the summary receiver operating characteristic (SROC) curve with the area under the curve (AUC) are preferred and were applied in the present analysis [28-30]. The graphical representations included boxes for summary sensitivity and specificity values, with horizontal lines showing confidence intervals (CIs). A DOR forest plot, combining sensitivity and specificity, was used to evaluate test accuracy. DOR values range from 0 to infinity, where higher values indicate better test performance. The sROC curve represented the performance of the diagnostic test. A guide for classifying diagnostic test accuracy based on the AUC is as follows: 0.90-1 (excellent), 0.80-0.90 (good),

Table1. General Characteristics of the Included Studies

	First author, reference number	Publication year	Country	Type of study	Type of radiotracer	Cancer type	Imaging technique	Number of patients (n)	Age range (y)	CASP score
1	Backhaus P. [35]	2022	Germany	R	[^{68}Ga]Ga-FAPI-46	Breast cancer	PET/MRI PET/CT	19	35-66	8.0
2	Guo W. [36]	2023	China	R	[^{68}Ga]Ga-FAPI-04 [^{18}F]F-FDG	Breast cancer	PET/CT	28	28-80	8.5
3	Kömek H. [37]	2021	Turkiye	P	[^{68}Ga]Ga-FAPI-04 [^{18}F]F-FDG	Breast cancer	PET/CT	20	32-65	8.5
4	Zheng S. [38]	2023	China	P	[^{68}Ga]Ga-FAPI-04 [^{18}F]F-FDG	Breast cancer	PET/CT	34	36-72	7.0
5	Chen J. [39]	2023	China	P	[^{68}Ga]Ga-FAPI-04 [^{18}F]F-FDG	Ovarian cancer	PET/CT	28	51-66	7.5
6	Lyu Y. [40]	2024	China	P	[^{68}Ga]Ga-FAPI-04 [^{18}F]F-FDG	Cervical cancer	PET/MRI PET/CT	25	18-75	8.0
7	Shu Q. [41]	2023	China	R	[^{68}Ga]Ga-FAPI-04 [^{18}F]F-FDG	Cervical cancer	PET/CT	35	30-76	7.0
8	Wegen S. [42]	2023	Germany	R	[^{68}Ga]Ga-FAPI-46 [^{18}F]F-FDG	Cervical cancer	PET/CT	7	43-67	8.0
9	Xi Y. [43]	2023	China	P	[^{68}Ga]Ga-FAPI-46 [^{18}F]F-FDG	Ovarian cancer	PET/MRI PET/CT	30	18-75	7.5
10	Zheng W. [44]	2023	China	R	[^{68}Ga]Ga-FAPI-04 [^{18}F]F-FDG	Ovarian cancer	PET/CT	27	35-84	7.5

CASP, Critical Appraisal Skills Programme; n, number; P, prospective; R, retrospective; y, year

0.70-0.80 (fair), 0.60-0.70 (poor) and 0.50-0.60 (failure) [31]. The data were analyzed using RStudio with the meta and mada packages [27, 28]. Examples of meta-analyses that have employed the same methodology include studies on melanoma screening, ultrasound for sarcopenia and COVID-19 testing [32-34]. Heterogeneity across studies was assessed using the I2 statistic. To explore potential publication bias, we constructed a funnel plot of the log diagnostic odds ratio (log(DOR)) versus its standard error for the primary diagnostic outcome across the included studies. Publication bias was not assessed for the detection of lymph node metastasis because of the limited number of studies. Formal sensitivity analyses and formal assessment of certainty were not conducted, given the minimal heterogeneity (I^2=0) and the limited number of included studies.

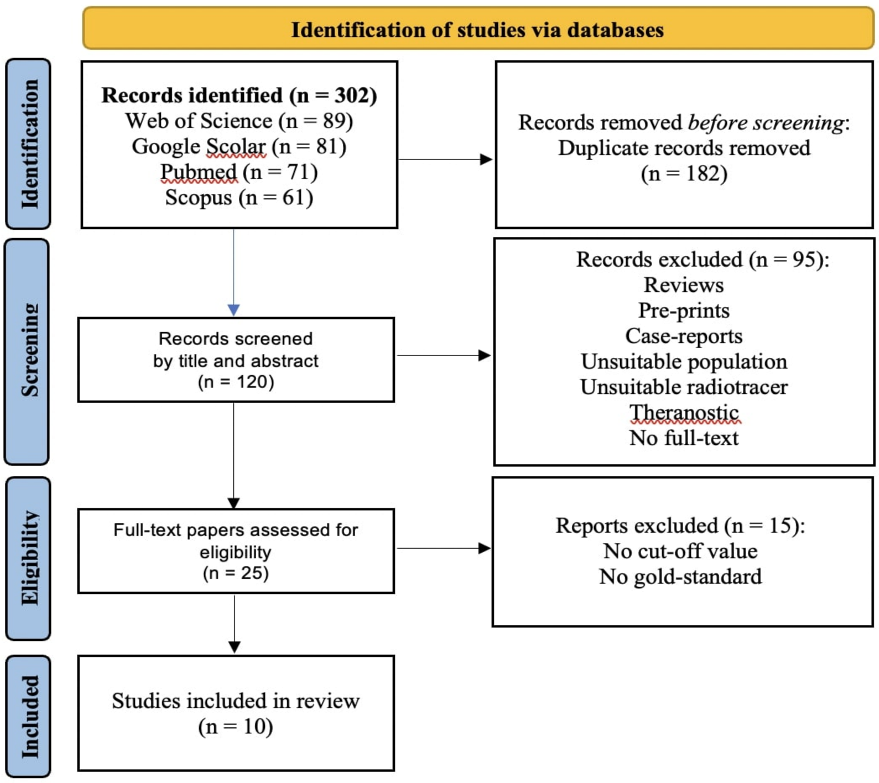

Figure 1. PRISMA Flow Chart

Results

The combined search in databases identified 302 publications. The majority of the included publications were retrieved from Web of Science and Google Scholar (29.5% and 26.8%, respectively; combined: 56.3%). Iterative deduplication designed to maximize the exclusion of replicate publications removed 182 (60.3%) publications. In addition, 120 publications proceeded to screening by title and abstract. Of these, 95 were excluded based on exclusion criteria. Overall, 25 publications were selected for full-text review and assessed for evidence synthesis suitability. Only 10 publications (40% of publications subjected to full-text review and assessment, or 8.3% of the 120 non-duplicates) were included in the qualitative analysis. The study selection flowchart is shown in Figure 1.

Qualitative analysis (systematic review)
Basic study and patient characteristics

The study design and patient characteristics are presented in Table 1. Overall, seven of the ten studies were conducted in China, two in Germany and one in Turkiye. All included studies were published in 2021-2024. A total of 253 patients were included in the 10 studies. [18F]F-FDG PET/CT and [68Ga]Ga-FAPI-04 PET/CT were analyzed in seven papers, [18F]F-FDG PET/CT and [68Ga]-FAPI-46 PET/MRI were analyzed in two papers, and [18F]F-FDG PET/CT and [68Ga]Ga-FAPI-04 PET/MRI were analyzed in one paper. Additionally, four papers focused on breast cancer, three papers on ovarian cancer and three on cervical cancer. The median sample size was 28 patients, ranging from 7 to 35 patients. Ages ranged from 18 to 84 years. Table 1 summarizes the general characteristics of the studies, including the first author, publication year, country, study type, radiotracer, cancer type, imaging technique, number of patients, age range, and CASP scores. The studies include both retrospective (R) and prospective (P) designs.

Technology

In nine out of ten studies, [18F]F-FDG PET/CT was performed first, followed by [68Ga]Ga-FAPI PET/CT and PET/MRI. Two groups of researchers, led by Lyu et al. and Xi et al., conducted a comparative analysis of [18F]F-FDG PET/CT and [68Ga]Ga-FAPI-46 PET/MRI [40, 43]. Furthermore, Xi et al. also carried out an additional examination performed by [18F]F-FDG PET/MRI of the abdomen and pelvis [43]. Bakhaus et al. evaluated the effectiveness of [68Ga]Ga-FAPI-46 PET/MRI in comparison to [68Ga]-FAPI-46 PET/CT [35].

Radiotracer activity varied among all papers, from 1.48 MBq/kg to 3.8 MBq/kg for [68Ga]Ga-FAPI, which was 3.7 times lower than the activity for [18F]F-FDG [35-44]. In some studies, the activity values were given as a general injected range [35, 38, 43]. Table 2 provides the technical characteristics of the studies, detailing the imaging techniques, injected activity presented in MBq or MBq/kg, time interval after injection, time interval between two techniques and the image analysis methods. Image analysis includes maximum standardized uptake value (SUV_{max}), TBR and tumor-to-liver ratio (TLR).

Outcomes specifying the detection rates of primary tumors and lymph node metastases are summarized in Table 3, which provides the type of parameter, number of lesions (n), true positives (TP), true negatives (TN), false positives (FP), false negatives (FN), sensitivity and specificity. Sensitivity and specificity are presented as percentages. "NA" indicates that data are not available.

Table 2. Technical Parameters of the Included Studies

	First author, reference number	Imaging modality	Injected activity	Time interval injection and image acquisition (min)	Time interval between two techniques (day)	Image analysis
1	Backhaus P. [35]	[68Ga]Ga-FAPI-46 PET/MRI [68Ga]Ga-FAPI-46 PET/CT	149 ± 48 MBq	55-128	Simultaneously	SUV_{max} TBR
2	Guo W. [36]	[68Ga]Ga-FAPI-04 PET/CT [18F]F-FDG PET/CT	1.8-2.2 MBq/kg 3.7 MBq/kg	60 60	1-6	SUV_{max} TBR
3	Kömek H. [37]	[68Ga]Ga-FAPI-04 PET/CT [18F]F-FDG PET/CT	2.0 MBq/kg 3.5-5.5 MBq/kg	60 60	<7	SUV_{max} TBR
4	Zheng S. [38]	[68Ga]Ga-FAPI-04 PET/CT [18F]F-FDG PET/CT	55.5-162.8 MBq 5.55 MBq/kg	21-34 48-71	7	SUV_{max} TBR
5	Chen J. [39]	[68Ga]Ga-FAPI-04 PET/CT [18F]F-FDG PET/CT	1.85 MBq/kg 3.7 MBq/kg	NA NA	<7	SUV_{max} TBR TLR
6	Lyu Y. [40]	[68Ga]Ga-FAPI-04 PET/MRI [18F]F-FDG PET/CT	1.48-2.22 MBq/kg 3.7-4.44 MBq/kg	NA NA	1-12	SUV_{max}
7	Shu Q. [41]	[68Ga]Ga-FAPI-04 PET/CT [18F]F-FDG PET/CT	1.85 MBq/kg 3.7 MBq/kg	45-60	<7	SUV_{max}
8	Wegen S. [42]	[68Ga]Ga-FAPI-46 PET/CT [18F]F-FDG PET/CT	2.04-3.8 MBq/kg 3.15-5.85 MBq/kg	50 71.5	<6	SUV_{max} TBR
9	Xi Y. [43]	[68Ga]Ga-FAPI-46 PET/MRI [18F]F-FDG PET/CT [18F]F-FDG PET/MRI	111-148 MBq 4.44-5.55 MBq/kg	30-40 40-60	<5	SUV_{max} TBR
10	Zheng W. [44]	[68Ga]Ga-FAPI-04 PET/CT [18F]F-FDG PET/CT	1.85-3.7 MBq/kg 3.7 MBq/kg	45-60 45-60	<7	SUV_{max} TBR

MBq, megabecquerel; MBq/kg, megabecquerels per kilogram; min, minutes; NA, not available; SUV_{max}, maximum standardized uptake value; TBR, tumor-to-background ratio; TLR, tumor-to-liver ratio

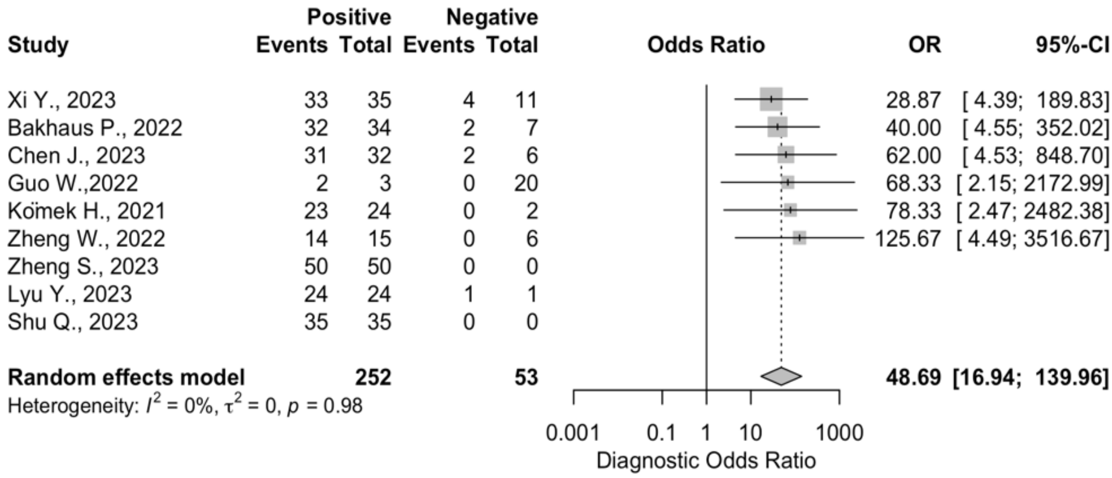

Figure 2. Diagnostic Odds Ratio for Detecting Primary Tumors with [^{68}Ga]Ga-FAPI PET Imaging in Breast, Ovarian and Cervical Cancers.

The highest sensitivity (100%) for detecting primary tumors is reported in five studies [36-38, 41, 44]. Shu et al. reported that all primary tumors were identified correctly, with no false negatives for either primary tumor or lymph node metastasis detection, resulting in 100% sensitivity [41].

Wegen et al. compared the effectiveness of [^{68}Ga]Ga-FAPI PET/CT with that of [^{18}F]F-FDG PET/CT for nodal staging in patients with cervical cancer and revealed 94.7% sensitivity and 100% specificity [42]. The lowest sensitivity for primary tumor detection (89.2%) was reported by Xi et al. [43], and the lowest specificity (71.4%) was reported by Bakhaus et al. [35].

Meta-analysis results

The meta-analysis included 10 publications focused on the detection rate of primary tumors and metastatic lesions through lesion-based assessment. In addition, nine out of ten studies were based on primary tumor performance analysis and seven out of ten studies were based on lymph node metastasis performance analysis.

Based on primary tumor performance analysis

In nine studies, the TP, TN, FP and FN rates for primary lesions detected by [^{68}Ga]Ga-FAPI PET imaging in breast, ovarian and cervical cancer patients were reported. Figure S1 presents the summary sensitivity and specificity of the studies that did not exhibit 100% values. Sensitivity ranged from 83% to 100%, while specificity ranged from 50% to 100% among the nine studies included in the present analysis [35-41, 43, 44].

The DOR for detecting primary lesions is summarized in a forest plot (Figure 2). The DOR of nine studies included in the subgroup of detecting primary tumors was high at 48.69, with a 95% CI of [16.94; 139.96]. The test for heterogeneity shows low heterogeneity with

Table 3. Outcomes for Patients

	First author, reference number	Lesion classification	Number of lesions (n)	TP (n)	TN (n)	FP (n)	FN (n)	Sensitivity (%)	Specificity (%)
1	Backhaus P. [35]	Primary tumor	41	32	5	2	2	94.1	71.4
2	Guo W. [36]	Primary tumor	23	2	20	1	0	100	95.2
3	Kömek H. [37]	Primary tumor	26	23	2	1	0	100	95.8
4	Zheng S. [38]	Primary tumor Lymph node mts	50 72	50 27	NA 42	NA 1	0 2	100 93.1	NA 97.7
5	Chen J. [39]	Primary tumor Retroperitoneal lymph node mts	38 186	31 185	4 NA	1 NA	2 1	93.9 99.5	80 NA
6	Lyu Y. [40]	Primary tumor Lymph node mts	25 25	24 2	NA 22	NA 0	1 1	96 66.7	NA 100
7	Shu Q. [41]	Primary tumor Lymph node mts	35 50	35 50	NA NA	NA NA	0 0	100 100	NA NA
8	Wegen S. [42]	Lymph node mts	22	18	3	0	1	94.7	100
9	Xi Y. [43]	Primary tumor Lymph node mts	46 61	33 52	7 6	2 0	4 3	89.2 94.5	80 100
10	Zheng W. [44]	Primary tumor Lymph node mts	21 76	14 76	6 NA	1 NA	0 0	100 100	85.7 NA

FN, false negative; FP, false positive; n, number; NA, not available; TN, true negative; TP, true positive

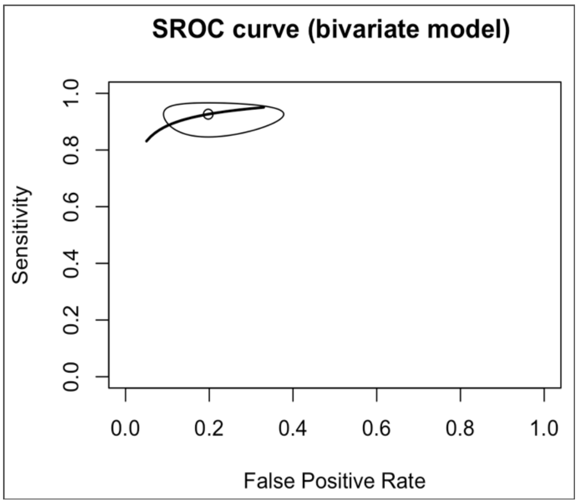

Figure 3. Ruecker-Schumacher (2010) SROC Curve for Evaluating Primary Tumors with [68Ga]Ga-FAPI PET Imaging in Breast, Ovarian and Cervical Cancers.

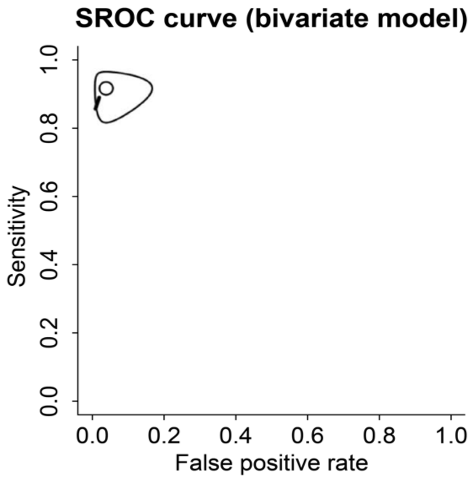

Figure 5. Ruecker-Schumacher (2010) SROC Curve for Evaluating Lymph Node Metastasis with [68Ga]Ga-FAPI PET Imaging in Breast, Ovarian and Cervical Cancers.

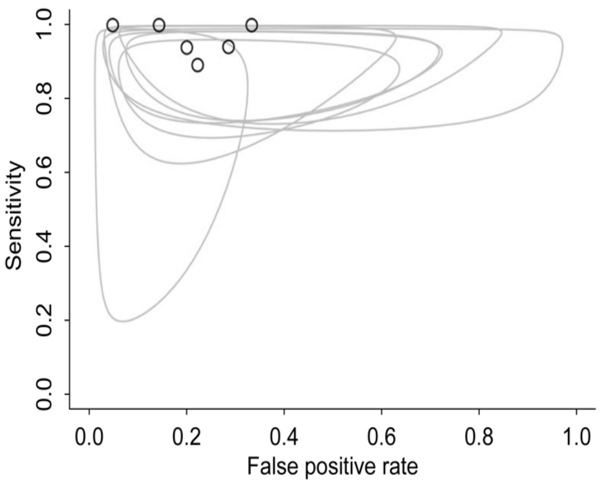

Figure 4. Confidence Regions on ROC space for detecting primary lesions with [68Ga]Ga-FAPI PET Imaging in Breast, Ovarian and Cervical Cancers.

I^2=0 (Figure 3). The funnel plot of the log(DOR) did not demonstrate clear asymmetry, although the small number of studies limits the reliability of this assessment (Figure S2).

Based on the AUC value of 0.94, the diagnostic performance of [68Ga]Ga-FAPI PET imaging for detecting primary tumors in female cancer is excellent. The sROC curve illustrates a minimal compromise between sensitivity and specificity across various threshold settings for [68Ga]Ga-FAPI PET. Additionally, the Confidence Regions on ROC space are all within the 0 to 1 range, further supporting the reliability of [68Ga]Ga-FAPI PET imaging in evaluating primary tumors. The sROC curve and confidence regions on ROC space are shown in Figure 3 and Figure 4, providing visual representations of the diagnostic efficacy of [68Ga]Ga-FAPI PET for primary tumors. The ROC curves illustrate a minimal compromise between sensitivity and specificity for [68Ga]Ga-FAPI PET/CT and [68Ga]Ga-FAPI PET/MRI in primary tumor detection (Figure 5).

Based on lymph node metastasis performance analysis

TP, TN, FP and FN rates for evaluating lymph node metastatic lesions by [68Ga]Ga-FAPI PET imaging in female cancer patients were reported in seven studies. Among these studies, sensitivity varied from 62% to 100% and specificity varied from 50% to 100% [38-44].

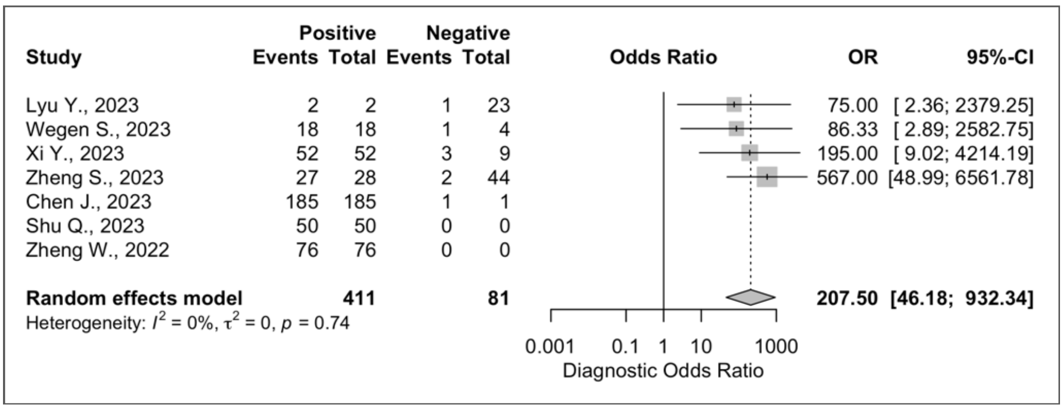

Figure 6. Diagnostic Odds Ratio for the Detecting Lymph Node Metastasis with [68Ga]Ga-FAPI PET Imaging in Breast, Ovarian and Cervical Cancers

Figure S3 presents the graphical view of the sensitivity and specificity observed in five studies that did not exhibit 100% values. The DOR of all seven studies in the meta-analysis was high at 207.50, with a 95% CI of [46.18; 932.34]. To evaluate the consistency of effect estimates across the included studies, we performed a heterogeneity test. The test for heterogeneity shows low heterogeneity, with $I^2=0$ (Figure 6).

The forest plot of the DOR for evaluating lymph node metastatic lesions using [68Ga]Ga-FAPI PET in breast, ovarian and cervical cancers is shown in Figure 6. The findings indicate excellent diagnostic performance based on an AUC of 96% for [68Ga]Ga-FAPI PET in detecting lymph node metastases. Additionally, the Confidence Regions on ROC space for detecting lymph node metastasis with [68Ga]Ga-FAPI PET imaging are within the 0 to 1 range, supporting the promising capability of the radiotracer for staging (Figure 7).

Discussion

This is the first study to estimate the effectiveness of [68Ga]Ga-FAPI PET for breast, ovarian and cervical cancer imaging using a meta-analysis. The data from nine studies indicate a high DOR of 48.69, with a 95% CI of [16.94; 139.96] for detecting primary tumors, and DOR of 207.50 with a 95% CI of [46.18; 932.34] in detecting lymph node metastasis. These findings support integrating [68Ga]Ga-FAPI PET into oncological practice, potentially improving the management of breast, ovarian and cervical cancer patients and impacting optimal treatment.

The outcomes of the present study support the results of the meta-analysis provided by Gege et al. on detecting peritoneal metastases, published in 2023. They included 11 publications targeting heterogeneous cancer and revealed a 99.9% pooled sensitivity for [68Ga]Ga-FAPI-04 PET/CT in lesion-based analysis among 4 publications [45]. The same pooled sensitivity was obtained from the first meta-analysis on the effectiveness of [68Ga]Ga-FAPI PET/CT, which included 14 publications [46]. The majority of the included studies concentrated on various cancer types, with none on breast or gynecological malignancies. In this regard, the current study presents a subgroup analysis of the diagnostic accuracy of [68Ga]Ga-FAPI PET specifically for breast, ovarian and cervical cancers. In our meta-analysis, the pooled sensitivity and specificity were not calculated because of significant heterogeneity among studies and the correlation between these metrics, as Shim et al. and Schlattmann et al. reported [29, 30]. Instead, DOR and sROC curves were utilized to provide a more accurate assessment of diagnostic performance for [68Ga]Ga-FAPI.

The accurate detection of lymph node status is crucial for cancer patients to ensure optimal therapy. Yang et al. studied the performance of [68Ga]Ga-FAPI-04 PET/CT for lung cancer in their systematic review and meta-analysis. Subgroup analysis showed high pooled sensitivity for [68Ga]Ga-FAPI-04 PET/CT in lung cancer (99%; 95% CI 90-100%) and non-small cell lung cancer (97%; 95% CI 86-100%) [47]. Ruan et al. [48] analyzed 14 studies with 358 gastric cancer patients to evaluate the role of [68Ga]Ga-FAPI PET imaging for gastric cancer, demonstrating suboptimal pooled sensitivity (72%) for detecting lymph node metastasis [95% CI: 67-78%] and high sensitivity for detecting peritoneal metastasis (98%) [95% CI: 92-100% . Nevertheless, these values were twice as high as those for [18F]F-FDG PET/CT [48]. These results might be associated with the histological features of the cancer and lymph node size [48]. The high pooled sensitivity of [68Ga]Ga-FAPI-04 PET/CT for detecting peritoneal lymph nodes might be related to the lower physiological accumulation of [68Ga]Ga-FAPI-04 in peritoneal organs and high levels of SUV_{max} and TBR levels. The DOR of [68Ga]Ga-FAPI PET for detecting lymph node metastasis in female cancer patients in our study was higher than for primary lesions.

The results of 10 original publications on [68Ga]Ga-FAPI PET were incorporated in this meta-analysis; however, the number of articles assessed for eligibility was higher. Some of them did not report numeral values of sensitivity and specificity. Conducting biopsies for all detected lesions using PET imaging might be impossible in some cases. This is the main reason why TP, TN, FP, and FN results were not always reported in published papers. Elboga et al. analyzed 48 patients with breast cancer of different subtypes and revealed that uptake values and TBR in [68Ga]Ga-FAPI-04 PET/CT were superior to those in [18F]F-FDG PET/CT [49]. The superior capability of [68Ga]Ga-FAPI-04 PET/CT for patients with invasive lobular carcinoma (ILC) was shown by Sahin et al. in their retrospective analysis [50]. Alçın et al. prospectively compared the effectiveness of [68Ga]Ga-FAPI-04 PET/CT and [18F]F-FDG PET/CT for initial staging in selected breast cancer patients with low FDG affinity [1]. [68Ga]Ga-FAPI-04 PET/CT demonstrated higher SUV_{max} values than [18F]F-FDG PET/CT. However, their findings were not included in our study because they lacked histological examination for all metastatic lesions.

There are several limitations to our study: 1) The limited sample size of included publications and patients and variability in cancer localizations may have impacted the validity of our outcomes. Although the exploratory funnel plot of log(DOR) did not demonstrate a clear asymmetry, the small number of studies limits the reliability of this assessment, and the presence of publication bias cannot be excluded. 2) Unclear time intervals between [68Ga]Ga-FAPI PET imaging and gold-standard examination in some included publications expose our study to various biases. 3) Half of the included studies were conducted retrospectively, increasing the risk of selection bias. 4) The imaging techniques and technical parameters across studies were not identical, leading to clinical heterogeneity. This limitation is critical because methodological differences can affect data comparability and the overall outcome. 5) The analysis focused on the clinical application of [68Ga]Ga-FAPI PET without considering a comparison to [18F]F-FDG. A comparison of these radiotracers could provide a comprehensive overview of each tracer's efficacy in different clinical settings.

One of the main avenues for future research is to conduct larger prospective studies. These studies should have a more homogenous sample, a larger cohort, and specific objectives. High-quality studies could enhance the perception of [68Ga]Ga-FAPI as a biomarker for various cancer types, potentially improving cancer management, including staging, restaging, prognosis, and outcomes for cancer patients.

In conclusion, [68Ga]Ga-FAPI has demonstrated high sensitivity and specificity in detecting primary tumors (DOR of 48.69, with a 95% CI of [16.94; 139.96]) and metastatic lesions (DOR of 207.50, with a 95% CI of [46.18; 932.34]) in breast, ovarian and cervical cancers. Based on the excellent diagnostic properties reveled in this meta-analysis, [68Ga]Ga-FAPI PET could provide accurate staging and restaging and play a key role in confirming treatment strategies for individual cases of female breast, ovarian and cervical cancers.

Author Contribution Statement

MG: Conceptualization, Methodology, Investigation, Formal Analysis, Writing – Original and draft preparation, Corresponding Author. AA: Resources, Data curation. UE: Validation, Resources, Revising. IK: Validation, Statistics, Writing – Review and Editing. GA: Formal analysis, Risk of bias assessment. ZZ: Software, Project Administration, Final Approval. JA: Resources, Validation, Risk of bias assessment, Writing – Review and Editing. ZhZh: Investigation, Supervision, Software, Final approval.

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Data Availability

The datasets generated and/or analyzed during the current study, as well as the raw data, are available from the corresponding author on reasonable request. The data supporting the findings of this study are also available within the article.

Study Registration

The study protocol has been registered with the PROSPERO International Prospective Register of Systematic Reviews (ID: CRD42024530820, https://www.crd.york.ac.uk/PROSPERO/view/CRD42024530820.

Conflict of Interest

None.

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