Diagnostic value of ^{18}F-FDG and ^{68}Ga-FAPI in head and neck cancers: A systematic review and meta-analysis

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Abstract

Objective: Gallium-68-labeled fibroblast activating protein inhibitor (^{68}Ga-FAPI) has been developed for positron emission tomography (PET) and proved to be a promising imaging agent. It has shown good diagnostic performance in the diagnosis of various solid tumors, including head and neck cancers (HNC). This study conducted a meta-analysis on the diagnostic performance of fluorine-18-fluorodeoxyglucose (^{18}F-FDG) and ^{68}Ga-FAPI in HNC, summarized the clinical evidence of ^{68}Ga-FAPI for HNC, and compared the diagnostic sensitivity of the two imaging agents in the primary and metastatic lesions of HNC. **Materials and Methods:** PubMed/ Medline, Embase and Cochrane Library databases were searched from built to 31 January 2023. Studies on patients with HNC underwent paired ^{18}F-FDG and ^{68}Ga-FAPI were included. Literature screening, full text review and data extraction were performed by 2 investigators. The risk of bias was examined with the QUADAS-2 tool. Meta-analysis of diagnostic test sensitivity was performed by a random-effect model and displayed by a forest plot. **Results:** A total of 507 studies were comprehensively retrieved, and 11 studies, 297 patients were selected for the systematic review and 9 studies for meta-analysis. Two hundred and nine patients selected for initial staging and 88 patients for recurrence. Pooled sensitivity at initial stage was conducted. Based on primary lesions, the sensitivity were ^{18}F-FDG 0.95 (0.81-0.99) vs ^{68}Ga-FAPI 0.99 (0.90-1.00). For lymph node metastases, based on patients, the sensitivity were ^{18}F-FDG 0.99 (0.77-1.00) vs ^{68}Ga-FAPI 0.92 (0.68-0.98); For distant metastases, based on patients, the sensitivity were ^{18}F-FDG 0.82 (0.03-1.00) vs ^{68}Ga-FAPI 0.92 (0.59-0.99). **Conclusion:** Gallium-68-FAPI has great potential in the diagnosis of HNC and has similar diagnostic value with ^{18}F-FDG. While there is much overlap in the performance (as measured by sensitivity) of these two agents but a trend may favor ^{68}Ga-FAPI over ^{18}F-FDG for detection of primary tumor and distant metastases. Therefore, in the diagnosis and evaluation of head and neck cancers, the combination of ^{68}Ga-FAPI and ^{18}F-FDG can be considered according to the individual situation.

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Introduction

Head and neck cancers (HNC) is a common cancer worldwide with 800,000 new cases and 500,000 deaths reported in 2020 [1], seriously threatening human health. Ninety percent are head and neck squamous cell carcinomas (HNSCC). The treatment depends on anatomical location, tumor stage and function [2, 3]. Most HNC are diagnosed at the advanced stage (III~IV) and overall survival rate is significantly lower than that at the early stage [4]. Being in the stage of late diagnosis is an important factor leading to the low survival rate. Therefore, early diagnosis is the key to reduce incidence rate and mortality. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is widely used for imaging of various tumors. However, there are still some limitations in HNC [5]. High ^{18}F-FDG uptake can be observed in some normal tissues, such as brain tissue, neck muscles, lymph nodes, tonsils, salivary glands, etc. Besides, false positive uptake may occur in some peritumoral inflammation or inflammatory reaction after surgery/radiotherapy, affecting the accuracy of diagnosis.

Tumor microenvironment (TME) plays an important role in the occurrence and development of head and neck squamous cell carcinomas (HNSCC), including cancer-associated fibroblasts (CAF) [6, 7]. Cancer-associated fibroblasts are fibroblasts with proliferation and migration characteristics, which can promote tumor growth, invasion, metastasis, angiogenesis and immunosuppression [8-10]. Fibroblast activation protein (FAP) is overexpressed on the cell membrane and matrix of CAF in various solid tumors, including HNC, and the expression is absent or low in healthy tissues [11, 12].

Gallium-68-conjugated fibroblast activation protein inhibitor (^{68}Ga-FAPI) has been developed for PET/CT or PET/magnetic resonance imaging (MRI) in vivo, targeting FAP and tumor interstitial visualization, showing good biological distribution characteristics and high tumor-to-background ratio (TBR) [13]. Previous studies show that FAPI has better diagnostic value than ^{18}F-FDG in different cancers [14, 15].

Some systematic reviews compared the diagnostic value of ^{18}F-FDG and ^{68}Ga-FAPI in the diagnosis of digestive system tumors, bone metastases, peritoneal metastases [16-19]. However, there is no separate meta-analysis to compare the diagnostic value of the two imaging agents in head and neck tumors. In this systematic review and meta-analysis, we aim to summarize the latest clinical evidence of the diagnostic value of ^{18}F-FDG and ^{68}Ga-FAPI in HNC.

Materials and Methods

This study is in agreement with the preferred reporting items for a systematic review and meta-analysis (PRISMA) statement [20].

Search strategy

A comprehensive search through the PubMed/Medline, Embase and Cochrane Library databases were carried out (from build to 31 January 2023). The following search terms were used: (A) 'PET' OR 'positron emission tomography' AND (B) 'FDG' OR 'fluorodeoxyglucose' AND (C) 'FAPI' OR 'FAP' OR 'fibroblast' AND (C) 'Head and neck' OR 'Nasopharyngeal' OR 'Oral' OR 'Oropharyngeal' OR 'Hypopharyngeal' AND(E) 'Cancer' OR 'Neoplasms' OR 'Tumors' OR 'Tumours' OR 'Carcinoma'. Studies written in English were included. To identify additional studies left out in the initial search, reference list of all selected articles were manually screened by two investigators (XX and XX).

Study selection

Two reviewers (XX and XX) screened the titles and abstracts independently. Articles met the inclusion criteria were systematically reviewed. The inclusion criteria were original articles evaluating the diagnostic efficacy of ^{18}F-FDG and ^{68}Ga-FAPI in HNC, including initial staging/restaging. Retrospective and prospective studies were included. Exclusion criteria were: (a) conferences, reviews, brief communications, abstracts, letters to the editor; (b) case reports or the head and neck tumor is only a subgroup of the original article and cannot be extracted for analysis;(c) patients in the studies didn't undergo paired ^{18}F-FDG and ^{68}Ga-FAPI; (d) studies evaluating ^{18}F-FDG and ^{68}Ga-FAPI not in head and neck cancers and studies applying imaging agents other than ^{68}Ga-FAPI. Studies with comprehensive data and provide enough raw data to complete a 2×2 contingency table [true positives (TP), false positives (FP), false negatives (FN), true negatives (TN)] were included in the meta-analysis. Disagreements were resolved in a consensus meeting.

Data extraction

Two reviewers independently performed the extraction. The following data were collected: authors, year of publication, country, tumor type, study design, age, sex ratio, diagnostic criteria, injection activity and the time interval between image acquisition, scan interval, image type, methods of image analysis, detection of lesions, the maximum standardized uptake value (SUVmax) in primary tumors, lymph node metastases and the distant metastases. Relevant authors were not contacted for unpublished data.

Quality assessment

The quality of the studies included was assessed according to the revised 'Quality Assessment of Diagnostic Accuracy Studies' tool (QUADAS-2) [21]. It was used to assess the risk of bias for the following criteria: patient selection, index test, reference test and flow/timing, whereas applicability concerns were assessed for patient selection, index test and reference test.

Statistical analysis

Stata 16.0 software was used for statistical analysis. Pooled sensitivities of ^{18}F-FDG and ^{68}Ga-FAPI were conducted (at least five studies per subgroup, including primary focus, lymph node metastases and distant metastases). A random-effect model analysis was performed to assess the summary sensitivity. Pooled data were given with 95% confidence intervals (95% CI) and displayed using forest plots. The evaluation of heterogeneity between studies is based on I2 and Q test statistics. Due to the limited clinical research at present, the heterogeneity may be affected by many factors, so further analysis of heterogeneity is not conducted. $I^2 \leq 75\%$ or $P<0.01$ is acceptable [22]. Publication bias was determined using the Deeks' funnel plot test, $P \geq 0.05$ means no obvious publication bias.

Results

Literature search

A total of 507 studies were comprehensively retrieved (Figure 1), excluding 96 repetitive searches. A total of 393 articles were excluded by reading the title and abstract. Through further reading the full text, two studies were not capable for meta-analysis, one article is about thyroid cancer [29], and the other is about negative ^{18}F-FDG [33]. Finally, eleven studies were included for systematic review, nine studies for meta-analysis [23-28, 30-32]. These studies provide reliable data to evaluate the accuracy of ^{18}F-FDG and ^{68}Ga-FAPI in the diagnosis of HNC.

Study and patient characteristics

Table 1 summarizes the main characteristics of the 11 studies included. All studies were published within the last 5 years. Seven studies (63.6%) were performed in China, three (27.3%) studies in Germany, one study (9.1%) in Thailand. Seven studies (63.6%) were prospective, while four (36.4%) were retrospective studies. Four (36.4%) studies had histopathology as the final diagnostic criterion, seven (9.1%) studies had histopathology or imaging (including CE-MRI/CT) as the final diagnostic criterion. Six studies (54.5%) were on patients for initial staging, one (9.1%) study on patients for reccurence detection and four (36.4%) studies on both. In 10 studies, the clinical stage criteria were according to the 8th edition of the American Joint Committee on Cancer (AJCC 8th edition) [34]. Patients in all studies underwent paired ^{18}F-FDG and ^{68}Ga-FAPI PET/CT or PET/MRI.

Technical aspects

The technical aspects of ^{18}F-FDG and ^{68}Ga-FAPI are summarized in Table 2. Patients in only 1 study underwent PET/MRI, while the other 10 studies used PET/CT. The activity standards injected were not uniform. Some studies reported the injection activity based on body weight, while others reported the total injection activity. Seven studies reported the uptake times were the same, ranging from 40-60 minutes, two studies were different while another two studies did not mention it. The scanning intervals were different in all, within 1 week in 7 studies, 2 weeks in 3 studies, the maximum is 59 days in 1 study. For image analysis, the SUVmax in all studies were measured. Visual evaluations were in 5 studies. The TBR were also used in 5 studies. In addition, the gross tumor volumes (GTV) based on the two imaging agents were also reported in 4 studies.

Main findings of qualitative assessment

A total of 11 studies, 297 patients with head and neck tumors were analyzed. Four studies (135 patients) on nasopharynx, two studies (46 patients) on oral cavity, one study (35 patients) on thyroid, one study (8 patients) on tonsil and three comprehensive studies (73 patients) on HNC. A total of 209 patients underwent ^{18}F-FDG and ^{68}Ga-FAPI for initial staging, 88 patients for recurrence detection. All studies evaluated the diagnostic value of two imaging agents in primary tumors and/or lymph node metastases and/or distant metastases.

Methodological quality of studies

Patient selection was the main source of bias among the 11 studies selected for the meta-analysis (Figure 2). Some studies did not mention whether the selected patients were continuous or random. In addition, some studies did not use the same reference standard, which would also increase the heterogeneity.

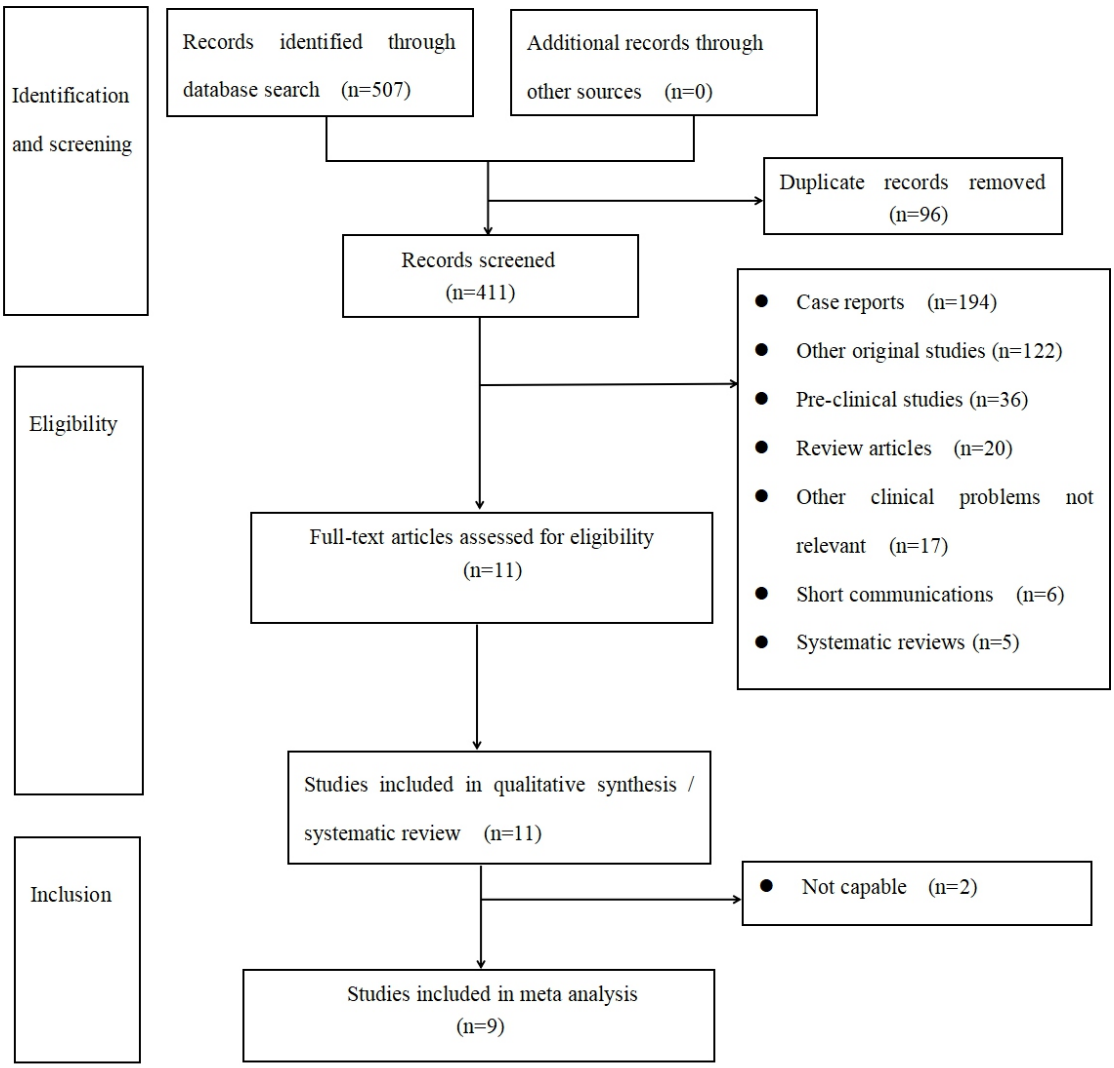

Figure 1. Flowchart of literature screening.

Table 1. Basic characteristics of the included studies.

Author and year	Study	Country	Tumor type	Patients (M/W)	Age (yr)	Diagnosis standard	Clinical staging criteria
Chunxia Qin 2021	P	China	Nasopharyngeal Carcinoma squamous cell carcinoma I: 3 II: 2 III: 8	15 (8:7) Initial staging: 14 Restaging: 1	51.2±9.4	Enhanced MRI	8^{th} AJCC
Liang Zhao 2021	R	China	Nasopharyngeal Carcinoma squamous cell carcinoma II: 5 III: 40	45 (35:10) Initial staging: 39 Restaging: 6	50 (25-70)	Enhanced MRI / Histopathology	8^{th} AJCC
Jieling Zheng 2022	P	China	Nasopharyngeal Carcinoma squamous cell carcinoma II: 2 III: 45	47 (32:15) Initial staging: 47 Restaging: 0	52.3±13.8	Enhanced MRI /Histopathology	8^{th} AJCC
Haoyuan Ding 2022	P	China	Nasopharyngeal Carcinoma squamous cell carcinoma I: 2 II: 11 III: 15	28 (5:23) Initial staging: 28 Restaging: 0	53±11	Enhanced MRI / Histopathology	8^{th} AJCC
Shaoming Chen 2022	P	China	Oral squamous cell carcinoma	36 (29:7) Initial staging: 36 Restaging: 0	62.5(34-87)	Histopathology	8^{th} AJCC
Christian Linz 2021	P	Germany	Oral squamous cell carcinoma	10 (8:2) Initial staging: 10 Restaging: 0	62±9	Histopathology	8^{th} AJCC

(Continued)

Hao Fu 2022	P	China	Thyroid Cancer papillar:32 follicular: 2 Hürthlecar Cinoma: 1	35 (18:27) Initial staging: 10 Restaging: 25	44 (28-58)	Histopathology and clinical follow-up	NR
S. Serfling 2020	R	Germany	Carcinomas of the Waldeyer's tonsillar ring squamous cell carcinoma	8 (2:6) Initial staging: 8 Restaging: 0	62(58-72)	Histopathology	8th edition of AJCC
Chetsadaporn Promteangtrong 2021	R	Thailand	HNSCC	40 (27:13) Initial staging: 12 Restaging: 28	56.65± 13.21	Histopathology/ Enhanced CT and MRI	8th edition of AJCC
Simone Wegen 2022	R	Germany	HNSCC: 14 Adeno: 1	15 (12:3) Initial staging: 0 Restaging: 15	66 (37-82)	Enhanced CT and/or MRI	8th edition of AJCC
Bingxin Gu 2021	P	China	Head and Neck Cancer of Unknown Primary HNSCC: 16 Adeno: 2	18 (16:2) Initial staging: 15 Restaging: 3	55(24-72)	Histopathology	8th edition of AJCC

P: prospective; R: retrospective; m/w: man/woman; yr: year; NR: not reported

Table 2. Technical aspects of imaging studies included in systematic review.

Author and year	Imaging modality	Injected activity (^{18}F-FDG)	Time interval (^{18}F-FDG injection and image acquisition)	Injected activity (^{68}Ga-FAPI)	Time interval (^{68}Ga-FAPI injection and image acquisition)	Interval between ^{18}F-FDG and ^{68}Ga-FAPI scans (days)	Image analysis
Chunxia Qin 2021	PET/MRI	3.7-5.4MBq/kg	60min	1.85-3.7 MBq/kg	30-60min	1 (1-3)	SUVmax/visual evaluation/GTV
Liang Zhao 2021	PET/CT	3.7MBq/kg	40min	1.8-2.2 MBq/kg	40min	2 (1-14)	SUVmax/GTV
Jieling Zheng 2022	PET/CT	2.96-4.44MBq/kg	60min	106.9± 29.6MBq	43.9±19.5min	<1week	SUVmax/ TBR/visual evaluation
Haoyuan Ding 2022	PET/CT	1.85MBq/kg	40-60min	3.7MBq/kg	40-60min	<1week	SUVmax/visual evaluation
Shaoming Chen 2022	PET/CT	2.96-3.70MBq/kg	60min	1.85-2.22 MBq/kg	60min	3 (1-5)	SUVmax/ TBR
Christian Linz 2021	PET/CT	204-317MBq	NR	66-168MBq	NR	4 (2-16)	SUVmax/ SUVpeak
Hao Fu 2022	PET/CT	3.7MBq /kg	60min	1.8-2.2 MBq/kg	60min	2 (1-6)	SUVmax/ Visual evaluation
S. Serfling 2020	PET/CT	292±32MBq	60min	145MBq	60min	<1week	SUVmax /TBR/ SUV max ratio/
Chetsadapon Prompteangtrong 2021	PET/CT	2.59MBq/kg	60min	2.0MBq/kg	60min	<2 week	SUVmax/ SUVmean/TBR /Visual evaluation/ FTV/TLF/MTV/ TLG
Simone Wegen 2022	PET/CT	263MBq	NR	147MBq	NR	4 (2-59)	SUVmax/ SUVmean/GTV
Bingxin Gu 2021	PET/CT	260.64± 40.81MBq	60min	143.71± 16.19MBq	60min	<1week	SUVmax /TBR/ SUVmax ratio/

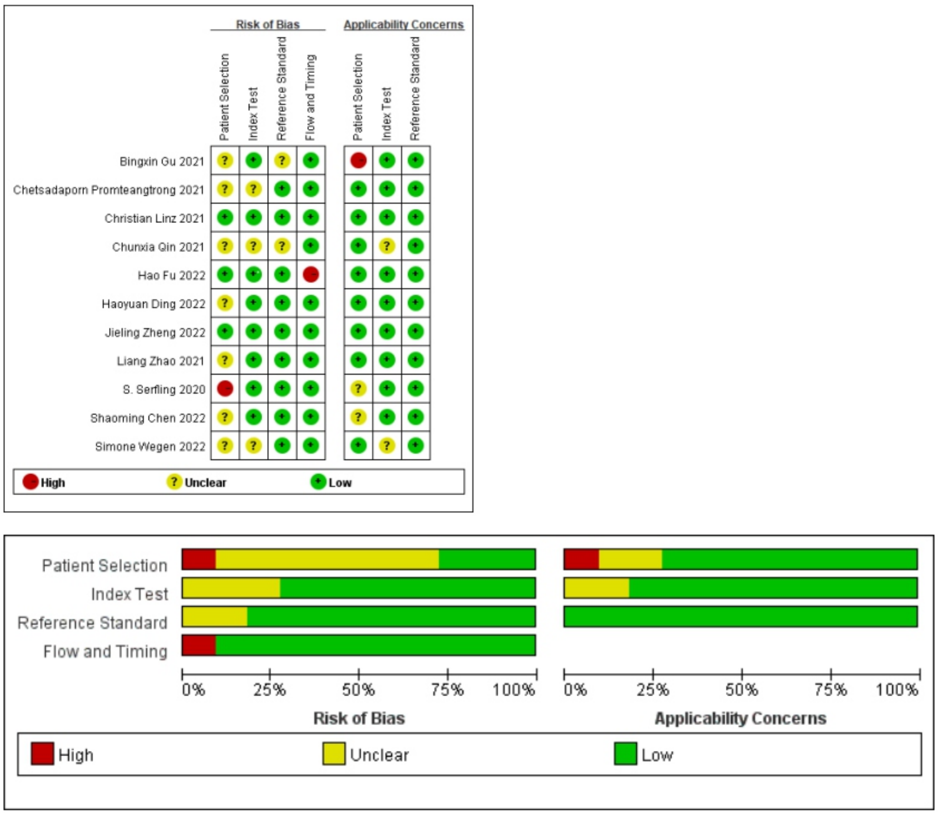

Figure 4. Risk bias evaluation of included studies.

Quantitative analysis (meta-analysis)

Nine studies were included and due to the incomplete true negative and false positive data associated with the included studies, it was not possible to analyze the specificity. So based on existing data, we just conducted the pooled sensitivity in patients at initial stage.

Primary tumor

Patient-based

A total of 217 people were evaluated the primary tumors, including 196 patients at initial stage and 21 patients with possible recurrence. For initial stage, ^{18}F-FDG detected 194 patients and ^{68}Ga-FAPI detected 196 patients. For recurrence, 20 patients were detected by ^{18}F-FDG and 21 by ^{68}Ga-FAPI. At both stages, ^{68}Ga-FAPI detected more patients than ^{18}F-FDG.

Lesion-based

A total of 551 lesions were located at the primary sites, 534 were primary and 17 were considered recurrence. Based on the forest plot (Figures 3a and 3b), in the initial primary tumor, the diagnostic sensitivity of ^{18}F-FDG was 0.95 (95% CI: 0.81-0.99; I^2=70.8%; P=0.00), ^{68}Ga-FAPI was 0.99 (95% CI: 0.91-1.00; I^2=27.6%; P=0.22). At initial stage, ^{68}Ga-FAPI was more sensitive than ^{18}F-FDG in the detection of primary lesions. Both ^{18}F-FDG and ^{68}Ga-FAPI detected 17 local recurrent lesions.

Node metastasis

Patient-based

A total of 162 patients had lymph node metastases, 121 patients for initial stage. Based on the forest plot (Figure 4a and 4b), the diagnostic sensitivity of ^{18}F-FDG was 0.99 (95% CI: 0.77-1.00; I^2=61.4%; P=0.02), ^{68}Ga-FAPI was 0.92 (95% CI: 0.68-0.98; I^2=00.0%; P=0.43). Testing 41 patients for restaging, ^{18}F-FDG detected 36 patients, while ^{68}Ga-FAPI detected 40 patients. At both cases, ^{18}F-FDG detected more patients with lymph node metastases than ^{68}Ga-FAPI.

Lesion-based

A total of 623 lymph node metastases, 548 were detected at the initial stage. The I^2 of ^{18}F-FDG and ^{68}Ga-FAPI were 94.8% and 88.7%. Due to the excessive heterogeneity based on the lesion, no pooled analysis was conducted. Seventy five were detected for restaging, ^{18}F-FDG detected 48, ^{68}Ga-FAPI detected 62. It was only reported in 2 articles, pooled analysis was not carried out. At initial stage, ^{18}F-FDG show better sensitivity than ^{68}Ga-FAPI, but for restaging, ^{68}Ga-FAPI detected more lymph node metastases.

Distant metastasis

Patient-based

A total of 20 patients had distant metastases, 12 patients at initial staging. Based on the forest plot (Figure 5a and 5b), the diagnostic sensitivity of ^{18}F-FDG was 0.82 (95% CI: 0.03-1.00; I^2=69.8%; P=0.02), ^{68}Ga-FAPI was 0.92 (95% CI: 0.59-0.99; I^2=00.0%; P=0.54). For restaging, it was only reported in 1 article, ^{18}F-FDG detected 7 patients, ^{68}Ga-FAPI detected 8 patients. At both cases, ^{68}Ga-FAPI detected more patients with distant metastases than ^{18}F-FDG.

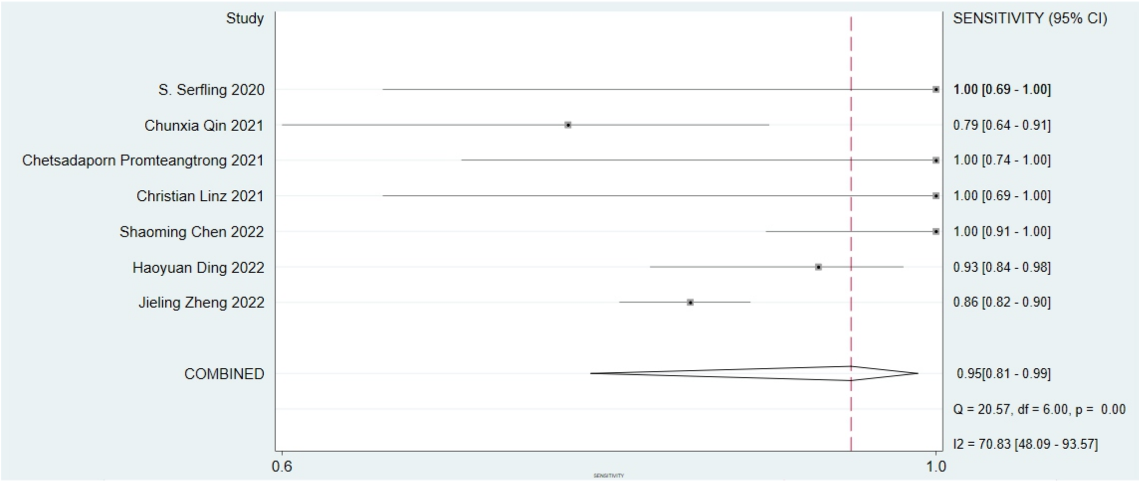

Figure 3a. The forest plot of ^{18}F-FDG and based on primary lesions.

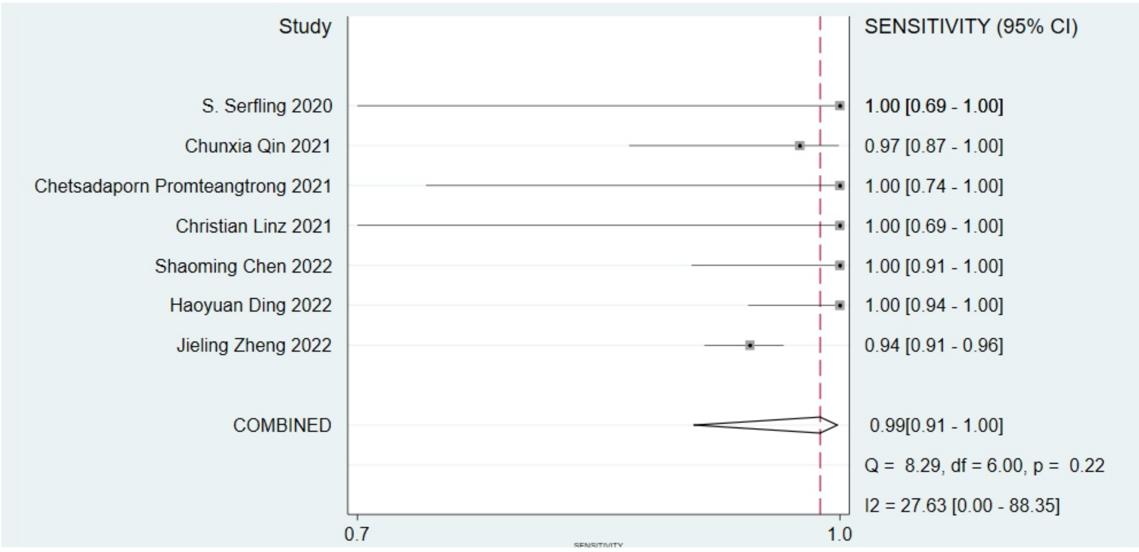

Figure 3b. The forest plot of ^{68}Ga-FAPI based on primary lesions.

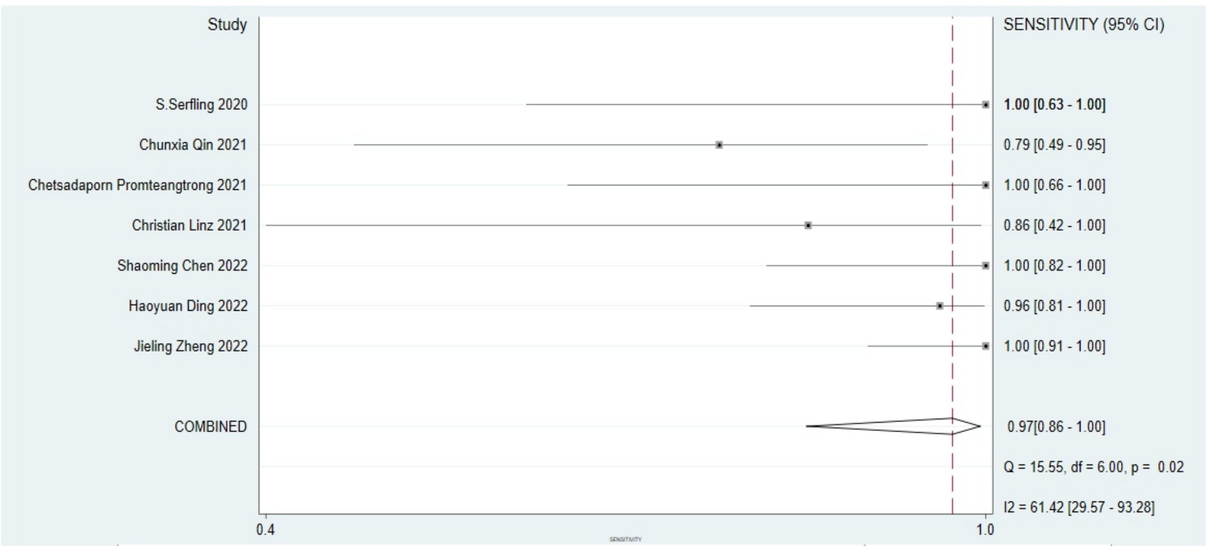

Figure 4a. The forest plot of ^{18}F-FDG based on patients (lymph node).

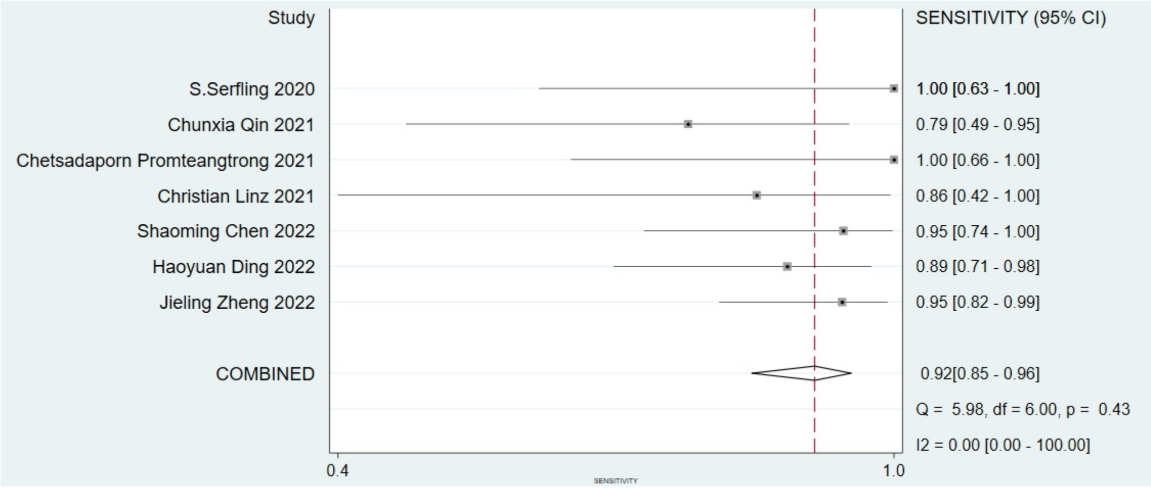

Figure 4b. The forest plot of ^{68}Ga-FAPI based on patients (lymph node).

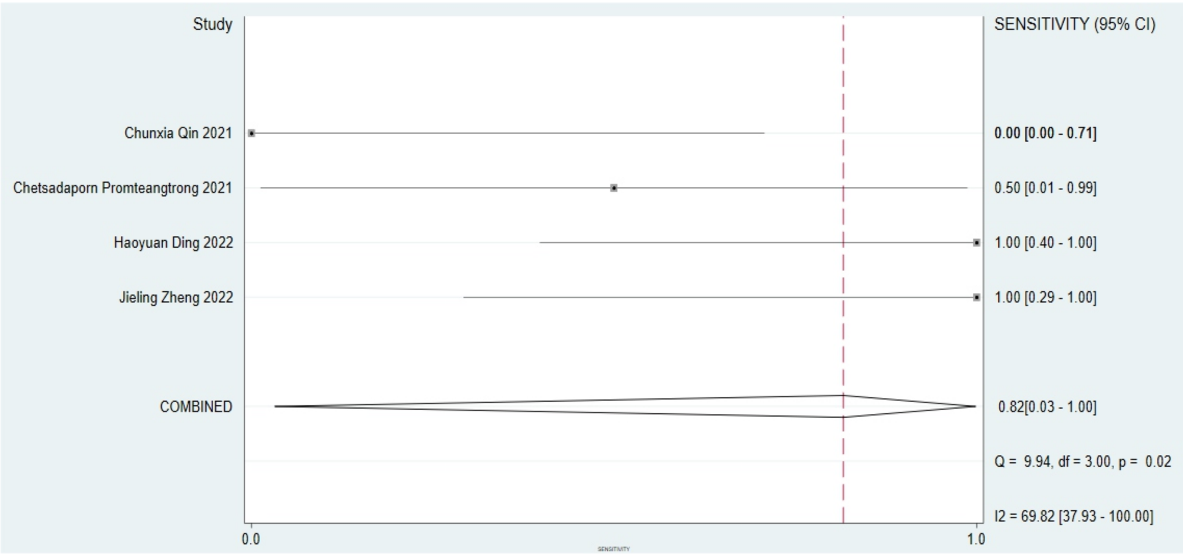

Figure 5a. The forest plot of ^{18}F-FDG based on patients (distant metastasis).

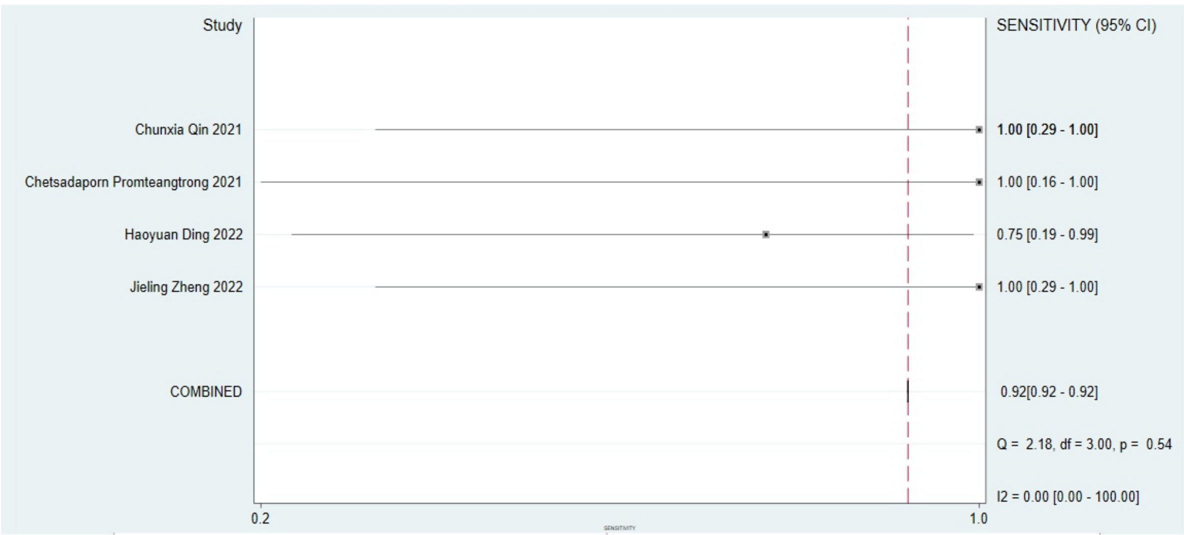

Figure 5b. The forest plot of ^{68}Ga-FAPI based on patients (distant metastasis).

Lesion-based

Hundred seventy four lesions were considered to be distant metastases in total, 64 in patients for initial staging. The I^2 of ^{18}F-FDG and ^{68}Ga-FAPI were 84.8% and 72.1%. Due to the excessive heterogeneity based on the lesion, no pooled analysis was conducted. For restaging, 110 distant lesions, ^{18}F-FDG detected 65 while ^{68}Ga-FAPI detected 87. Gallium-68-FAPI detected more distant metastases than ^{18}F-FDG at both cases.

Publication bias

The Deeks' funnel plot tests showed there was no obvious publication bias. For primary tumor, based on lesions, the P of ^{18}F-FDG and ^{68}Ga-FAPI were 0.78 and 0.39; for node metastasis, based on patients, the P of ^{18}F-FDG and ^{68}Ga-FAPI were 0.01 and 0.33; for distant metastasis, based on patients, the P of ^{18}F-FDG and ^{68}Ga-FAPI were 0.52 and 0.06, respectively.

Discussion

Fluorine-18-FDG PET/CT has been recommended for the initial staging of advanced HNSCC - stage (III-IV), detecting distant metastases with a high accuracy [35]. As a new imaging agent, ^{68}Ga-FAPI has shown considerable diagnostic value in many cancers in recent studies. In our study, we found FAPI may show unique diagnostic value for HNC.

In primary tumors, the sensitivity of ^{18}F-FDG was lower than ^{68}Ga-FAPI. Six studies reported the SUVmax of ^{68}Ga-FAPI in primary lesions was higher than ^{18}F-FDG (Table 3). The current research results are inconsistent as to whether there is a correlation between the uptakes of the two. One study showed that higher invasiveness of tumors was accompanied by higher glycolysis and higher CAF activity [26], but two studies showed there was no correlation between them [23, 30]. Various types of solid tumors have different loads, like different pathological types and sizes of tumors have different biological activities may reflect different glucose utilization and CAF activity. In half studies, ^{68}Ga-FAPI showed better TBR than ^{18}F-FDG, which was consistent with previous study [14]. Due to its high physiological activity in normal brain tissue, ^{18}F-FDG cannot evaluate well the skull base and assess possible intracranial invasion in patients with advanced stage. In four studies on nasopharyngeal carcinoma, ^{68}Ga-FAPI better detected the skull base and intracranial invasion than ^{18}F-FDG, thus changing the T stage of patients.

In addition, 44%-75% patients [36, 37] with head and neck cancer of unknown primary (HNCUP) cannot be found by ^{18}F-FDG. In Gu et al. (2022) [33] ^{68}Ga-FAPI detected 7/16 patients with negative ^{18}F-FDG, so ^{68}Ga-FAPI may provide additional value in HNCUP patients. In the detection of local recurrence, the two imaging agents showed similar detection, but the number was small. In addition, it was observed [24] when detecting local recurrence, patients usually undergo surgery or radiotherapy before, which may lead to local inflammation and tissue fibrosis, leading to false positive ^{18}F-FDG and ^{68}Ga-FAPI. Therefore, nuclear medicine physicians and radiologists should be more careful when diagnosing recurrence and pay attention to the selection of the time point for efficacy evaluation after treatment.

Immunohistochemistry (IHC) analysis of FAP was performed in 3 studies. Serfling et al. (2021) found FAP was positive in all primary tumors and all metastatic lymph nodes except one patient. The volume of metastatic lymph nodes was positively correlated with the immunohistochemical score of FAP, and ^{68}Ga-FAPI was negative in more metastatic lymph nodes with FAP 1+ instead of higher score (2+- 3+) [30]. It was found [27] the SUVmax of ^{18}F-FDG and ^{68}Ga-FAPI were positively correlated with tumor size, this was consistent with the results of a recent prospective study [38]. They analyzed the correlation between the biological distribution of ^{68}Ga-FAPI-46 PET and the expression of FAP in cancer and its adjacent non-cancer tissues in 114 patients, involving 14 types of cancer. The results showed the FAP IHC score was positively correlated with the SUVmax and SUVmean of ^{68}Ga-FAPI-46, with significant difference. In addition, the size of tumor tends to be positively correlated with SUVmax and SUVmean. FAP 1+~3+ scores expression was found in primary tumors and lymph node metastases in two studies [25, 28]. However, in Zheng et al. (2022), FAP was mainly located in CAF near tumor cells, and FAP was not expressed in cancer cells and/or other stromal cells, the IHC score of FAP was not related to SUVmax of ^{68}Ga-FAPI and tumor size. Due to the small sample, the difference of tumor type and the deviation of sampling, the relationship among the expression of FAP, the biological distribution of ^{68}Ga-FAPI and the tumor size still needs to be further explored in the future.

Radiotherapy is important for HNC, which significantly improves the overall survival rate. Insufficient resection margin, tumor radiation resistance and initial treatment dose, lead about 50% of patients at high-risk stage to tumor recurrence within the target volume of radiotherapy or its edge within 3 years [39]. Therefore, it is important to establish an appropriate target volume for precise radiotherapy. Fluorine-18-FDG PET/CT has been increasingly used to guide the delineation of radiotherapy target areas for HNC [40]. We found ^{68}Ga-FAPI had a higher TBR than ^{18}F-FDG, which could better distinguish the invasion range of local tumors from surrounding normal tissues. A study explored the use of ^{68}Ga-FAPI PET/CT to create the gross tumor volume (GTV) of HNC for radiotherapy. They found, compared with conventionally created GTV (based on imaging information from MRI and CT), FAPI-based GTVs were significantly larger. Especially, the ^{68}Ga-FAPI-based GTV were greater by ^{68}Ga-FAPI×3 threshold than all other GTV [41]. The clinical application of ^{18}F-FDG and ^{68}Ga-FAPI PET for tumor volume delineation was performed in 4 studies. In three studies, based on the same threshold, the FAPI-based GTV were all larger than the ^{18}F-FDG-based GTV. The possible reason is ^{18}F-FDG reflects the glucose utilization of solid tumors, and ^{68}Ga-FAPI reflects the activity of CAF around tumors, so it can better display the tumor load range. In Qin et al. (2021) [23] the delineation volume based on ^{68}Ga-FAPI 25% SUVmax and ^{18}F-FDG 20% SUVmax had credibility and consistency level with MRI. Besides, Wegen et al. (2022) [32] had the same findings with Syed et al. (2020) Some patients had ^{68}Ga-FAPI uptake in the primary tumor regions, which would not have been covered by the CT-GTV or CT-planning tumor volume (PTV). This means the radiothe-

Table 3. *Uptake of ¹⁸F-FDG and ⁶⁸Ga-FAPI in primary tumors.*

Author and year	SUVmax ^{18}F-FDG	SUVmax ^{68}Ga-FAPI	P	Visual evaluation of primary tumor invasion			
				Nasopharynx ^{18}F-FDG ^{68}Ga-FAPI MRI	Parapharyngeal space ^{18}F-FDG ^{68}Ga-FAPI MRI	Skull base bone ^{18}F-FDG ^{68}Ga-FAPI MRI	Intracalvarium ^{18}F-FDG ^{68}Ga-FAPI MRI
Chunxia Qin 2021	17.73±6.84	13.87±5.13	0.078	14 15 15	10 12 12	7 7 8	0 4 4
Liang Zhao 2021	10.11 (1.83-19.42)	16.18 (7.48-34.50)	<0.001	- - -	- - -	- - -	- - -
Jieling Zheng 2022	13.2±6.0	11.3±5.3	0.107	50(p)50(p) 50(p)	83(p)82(p) 89(p)	177(p)207(p)138(p)	5(p)15(p)19(p)
Haoyuan Ding 2022	11.7±4.6	12.1±4.9	0.543	27 28 28	18 18 18	11 11 11	1 4 4
				^{18}F-FDG (p)		^{68}Ga-FAPI (p)	
Shaoming Chen 2022	11.77±3.99	12.74±3.51	0.136	Tongue:18 Floor of mouth:6 Buccal mucosa:5 Gingiva:5 Palate:3		Tongue:18 Floor of mouth:6 Buccal mucosa:5 Gingiva:5 Palate:3	

(continued)

Christian Linz 2021	25.5±13.2	20.8±6.4	0.09	Tongue:2 floor of the mouth:5 maxillary mucosa:1 alveolar process of Mandible:2	Tongue:2 floor of the mouth:5 maxillary mucosa:1 alveolar process of Mandible: 2
Hao Fu 2022	6.1 (3.4-27.0)	12.6 (9.4-16.9)	0.72	Thyroid: 4	Thyroid: 4
S. Serfling 2020	21.29±7.97	16.06±6.29	0.2	Waldeyer's tonsillar ring: 10	Waldeyer's tonsillar ring: 10
Chetsadaporn Promteangtron g 2021	18.59±9.61	19.28±7.45	0.65	Tongue: 7 Pyriform: 5 BOT: 3 Nasopharynx: 18 Nasal cavity: 1 Lip: 1 Oropharynx: 1 External ear canal: 1 Retromolar trigone: 1 Oral mucosa: 1 Glottis: 1 Floor of mouth: 1 Retromolar trigone: 1	Tongue: 7 Pyriform: 5 BOT: 3 Nasopharynx: 18 Nasal cavity: 1 Lip: 1 Oropharynx: 1 External ear canal: 1 Retromolar trigone: 1 Oral mucosa: 1 Glottis: 1 Floor of mouth: 1 Retromolar trigone: 1
Simone Wegen 2022	13.4 (5.68, 21.9)	14.8 (9.26, 26.6)	0.28	Nasopharynx: 3 Oropharynx: 8 Hypopharynx: 1 Larynx: 3	Nasopharynx: 3 Oropharynx: 8 Hypopharynx: 1 Larynx: 3
Bingxin Gu 2021	-	8.79 (2.60-16.50)		-	Nasopharynx: 1 Palatine tonsil: 2 Submandibular: 2 Hypopharynx: 2

-: none; n: number of lesions; p: patients

rapy GTV for head and neck tumors based on ^{68}Ga-FAPI has great potential. However, there are few relevant studies at present and the precise definition of GTV still needs to be further explored and clarified.

In lymph node metastases, ^{18}F-FDG showed higher sensitivity than ^{68}Ga-FAPI at initial stage. For recurrence, ^{68}Ga-FAPI detected more lymph node metastases. In six studies, the SUVmax of ^{68}Ga-FAPI in metastatic lymph nodes were higher than that of ^{18}F-FDG (Table 4). As to cervical metastatic lymph nodes, some studies reported the sensitivity and specificity of ^{18}F-FDG PET/CT were 68.8% and 85.1% [42]; 89.5% and 95.2% of ^{18}F-FDG PET/MRI [43]. Lymph node metastases are common in HNC. Early detection and proper treatment of cervical lymph node metastases are crucial to prognosis. In our study, ^{18}F-FDG showed a higher detection rate in lymph node metastases. However, because no biopsy was taken for each lymph node and the criteria for determining lymph node metastasis were different, besides, due to the high incidence of cervical lymphadenitis and reactive hyperplasia, there may be false positive lymph nodes with ^{18}F-FDG positive but ^{68}Ga-FAPI negative. The specificity cannot be analyzed and summarized in our study, but four studies [27-30] carried out pathological biopsies of cervical lymph nodes and found that ^{18}F-FDG has higher false positive uptake and worse specificity. Therefore, this conclusion should be carefully considered when extrapolating. Combined diagnosis of ^{18}F-FDG and ^{68}Ga-FAPI can better help to manage the N stage of patients.

In distant metastases, based on patients, ^{68}Ga-FAPI showed higher sensitivity than ^{18}F-FDG in initial stage. For restaging, ^{68}Ga-FAPI still detected more distant metastases. Of the 7 studies reported distant metastases, 5 showed the SUVmax of ^{68}Ga-FAPI was higher than ^{18}F-FDG (Table 5). In all studies, bone metastases were the most frequently detected, the SUVmax of ^{68}Ga-FAPI is all higher than ^{18}F-FDG in bone lesions. This is similar to the existing meta-analysis results [18] which showed ^{68}Ga-FAPI-04 had a higher sensitivity for bone metastases than ^{18}F-FDG, while ^{18}F-FDG has a higher specificity. In bone benign/malignant tumors, FAP is positive, which may be related to activated fibroblasts and/or myofibroblasts [44]. Therefore, ^{68}Ga-FAPI may appear false positive uptake on benign bone lesions when judging bone metastases.

Table 4. *Uptake of ^{18}F-FDG and ^{68}Ga-FAPI in lymph node metastasis.*

Author and year	SUVmax ^{18}F-FDG	SUVmax ^{68}Ga-FAPI	P	Positive lymph nodes (^{18}F-FDG)	Positive lymph nodes (^{68}Ga-FAPI)	P	Positive lymph nodes (MRI vs Histopathology)
Chunxia Qin 2021	11.94±6.15	8.81±3.79	<0.001	100	48	NR	NR
Liang Zhao 2021	11.12	6.53	<0.001	91	115	<0.001	118 (MRI)
Jieling Zheng 2022	8.1±4.8	7.1±3.6	0.003	393	255	<0.001	348 (MRI)
Haoyuan Ding 2022	13.6±5.5	11.7±5.0	0.133	228	263	NR	262 (MRI)
Shaoming Chen 2022	11.77 ±3.99	2.74±3.51	0.136	69	43	NR	46 (Histopathology)
Christian Linz 2021	14.9±12.3	10.7±6.9	0.09	14	13	NR	16 (Histopathology)

(Continued)

Hao Fu 2022	Neck: (Central compartment): 5.0 (1.5-24.0)	Neck: (Central compartment): 8.3 (3.1-19.9)	P=0.22	47	61	NR	74 (Histopathology)
	(Lateral compartment): 9.0 (4.7-16.9)	(Lateral compartment): 3.5 (1.0-21.9)	P=0.001				
	Axillary: 4.3 (2.2-5.2)	Axillary: 8.5 (1.3-12.8)	P=0.01				
	Mediastinal: 5.0 (1.6-13.3)	Mediastinal: 9.1 (1.8-21.2)	P=0.001				
	Abdominal: 7.9 (2.8-16.2)	Abdominal: 9.0 (4.9-11.0)	P=0.47				
S. Serfling 2020	NR	NR	NR	14	8	NR	17 (Histopathology)
Chetsa-daporn Promtean-gtrong 2021	Total: 12.55±6.68	Total: 15.04±10.25	P=0.08	128	94		
	Neck: 13.67±7.38	Neck: 16.91±9.35					
	Supraclavicular: 9.97±3.47	Supraclavicula:7. 16±2.01					
	Axillary:18.64	Axillary:10.98					
	Mediastinal: 9.21±4.22	Mediastinal: 8.64±4.54					
	Abdominal: 15.83±7.02	Abdominal: 31.84±9.00					
Simone Wegen 2022	6.17 (1.73-20.9)	9.47 (1.83-24.9)	0.1	NR	NR	NR	NR
Bingxin Gu 2021	9.05±5.29	9.08±4.69	0.975	65	65	NR	NR

Table 5. *Uptake of ^{18}F-FDG and ^{68}Ga-FAPI in distant metastasis.*

Author and year	SUVmax ^{18}F-FDG	SUVmax ^{68}Ga-FAPI	P	Positive metastases lesions (^{18}F-FDG)	Positive metastases lesions (^{68}Ga-FAPI)
Chunxia Qin 2021	NR	NR	NR	0	4 small skull lesions 3; Pons 1
Liang Zhao 2021	3.11 (0.66-13.33)	6.94 (3.01-20.41)	<0.001	19 bone 7; lung 2; liver 8; peritoneum 2	41 bone 19; lung 4; liver 16; peritoneum 2
Jieling Zheng 2022	8.3±4.4	5.3±2.9	0.890	11 bone 10; liver 1	11 bone 11
Haoyuan Ding 2022	8.3±5.9	6.6±4.0	0.450	7 lung 3; bone 4	5 lung 1; bone 4
Shaoming Chen 2022	-	-	-	-	-
Christian Linz 2021	-	-	-	-	-
Hao Fu 2022	Pulmonary : 1.1 (0.5-7.5)	Pulmonary : 1.7 (0.6-12.8)	0.004	65	87
	Bone : 5.3 (4.5-8.0)	Bone : 6.0 (3.8-20.3)	0.50		
	Other sites: 5.3 (4.5-6.2)	Other sites: 9.1 (2.6-9.9)	0.29		
S. Serfling 2020	-	-		-	-
Chetsadaporn Promteang-trong 2021	13.59±7.64	16.89±9.96	0.09	NR	NR
Simone Wegen 2022	Visceral : 5.57 (2.62, 11.1)	Visceral: 7.05 (1.80, 25.0)	0.46	NR	NR
	Bone : 2.59 (1.41, 2.75)	Bone : 7.45 (4.00, 14.2)	0.25		
Bingxin Gu 2021	Bone: 8.11±3.00	Bone: 6.96±5.87	0.478	Bone: 17	Bone: 17

Limitations

There are some limitations. Firstly, the original studies that can be included and analyzed are insufficient, and the types of HNC included are not comprehensive. Limited by many factors, there are few data about true negative, it is impossible to study and analyze the specificity and accuracy, so the conclusions drawn may not be comprehensive. In the future, more high-quality multicenter prospective research is still needed. Nevertheless, this is the first systematic review to compare and evaluate the diagnostic value of ^{18}F-FDG and ^{68}Ga-FAPI in HNC, which can provide some evidence-based medical evidence for clinicians/radiologists in the diagnosis and treatment.

In conclusion, ^{68}Ga-FAPI has great potential in the application of HNC. It shows similar diagnostic performance with ^{18}F-FDG, while there is much overlap in the performance (as measured by sensitivity) of these two agents but a trend may favor ^{68}Ga-FAPI over ^{18}F-FDG for detection of primary tumor and distant metastases. Therefore, ^{68}Ga-FAPI can be used as a supplementary detection method for ^{18}F-FDG in head and neck tumors.

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