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Diagnostic accuracy of F-18 FDG PET or PET/CT for detection of lymph node metastasis in clinically node negative head and neck cancer patients; A systematic review and meta-analysis

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ABSTRACT

Objective: The purpose of the current study was to investigate the diagnostic performance of F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) or positron emission tomography/computed tomography (PET/CT) for the detection of cervical lymph node (LN) metastasis in clinically node negative head and neck squamous cell cancer (cN0 HNSCC) patients through a systematic review and meta-analysis.

Methods: The PubMed and EMBASE database, from the earliest available date of indexing through April 30, 2018, were searched for studies evaluating the diagnostic performance of F-18 FDG PET or PET/CT for the detection of LN metastasis in cN0 HNSCC patients. We determined the sensitivities and specificities across studies, calculated positive and negative likelihood ratios (LR+ and LR−), and constructed summary receiver operating characteristic (SROC) curves.

Results: Across 18 studies (1044 patients), the pooled sensitivity for F-18 FDG PET or PET/CT for the detection of LN metastasis was 0.58 and a pooled specificity of 0.87 for patient based analysis. Neck side based analysis showed the pooled sensitivity of 0.67 and a pooled specificity of 0.85. Level based study demonstrated the pooled sensitivity of 0.53 and a pooled specificity of 0.97 (95% CI; 0.95–0.98). In meta-regression analysis, no definite variable was the source of the study heterogeneity.

Conclusion: The current meta-analysis showed the low sensitivity and moderate specificity of F-18 FDG PET/CT for the detection of cervical LN metastasis in cN0 HNSCC patients. Level based analysis of F-18 FDG PET or PET/CT has a high specificity and NPV for the detection of cervical metastatic LN detection.

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is the eighth most common malignancy in male in the United States [1]. In 2018, an estimated 37,160 men will be diagnosed with HNSCC [1]. The presence of cervical lymph node (LN) metastasis is one of the most important prognostic factors in HNSCC and has a great impact on patient's treatment and prognosis [2]. Therefore, it is great important to know the exact status of cervical LN involvement of HNSCC to provide the effective treatment.

Generally, clinical examination such as neck palpation, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US) with US guided fine needle aspiration cytology (FNAC) are commonly used for cervical LN staging. However, the detection of occult LN metastasis in clinically node negative (cN0) HNSCC patients remains a diagnostic challenge. The prevalence of occult cervical LN metastasis is known to range from 12% to 50% depending on the location and the size of the primary cancer [3,4]. Also, the presence of occult metastasis increases the risk of recurrence and possess the poor prognosis [5].

Currently, the treatment of cN0 HNSCC remains controversial. Although previous study suggested improved survival rates in patients who receive elective neck dissection [6], the treatment is usually determined by the possibility of cervical LN metastasis. Therefore, elective neck dissection should be performed if the risk of occult metastasis is thought to be > 15% to 20%.

The CT and MRI are generally used to assess the primary tumor and LN status in HNSCC patients. However, these imaging techniques have

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Table 1
Characteristics of the included studies.

Authors	Year	Study origin	Study design	Analysis	Patient number	M/F	Age (range)	F-18 FDG (MBq)	Interpretation criteria of PET or PET/CT	Diagnosis of LN metastasis
Brouwer J	2004	Netherlands	R	NSB	15	NR	NR	370	VA	HP
Cetin B	2013	Turkey	R	PB	36	23/13	55 (21–75)	3.7 MBq/kg	VA	HP
Chauhan A	2012	India	P	NSB	49	37/12	59.4 (42–82)	370	VA	HP
Chaukar D	2016	India	P	NSB	70	58/12	51 (29–71)	370	VA	HP
Krabbe CA	2008	Netherlands	R	PB	38	21/17	59	NR	VA	HP
Lee HJ	2015	Korea	R	PB, LB	39	36/3	65.4 (39–82)	5.5 MBq/kg	VA	HP
Myers LL	1998	USA	R	NSB	14	NR	61.3 (43–72)	370	VA	HP
Nahmias C	2007	USA	R	PB	70	36/34	(29–89)	370	VA	HP
Ng SH	2006	Taiwan	P	PB, LB	134	129/5	52.1 (26–82)	370	VA	HP
Ozer E	2012	Turkey	R	NSB	112	NR	NR	555	VA	HP
Roh JL	2014	Korea	P	PB, NSB, LB	91	57/34	59 (28–84)	370	VA	HP
Schöder H	2006	USA	P	NSB, LB	31	21/10	60 (37–84)	555	VA	HP
Schroeder U	2008	Germany	R	PB	17	11/6	58 (36–84)	370	VA	HP
Sohn B	2016	Korea	R	PB, LB	49	42/7	59.1 (31–85)	5.5 MBq/kg	VA	HP
Stoeckli SJ	2002	Switzerland	R	PB	12	10/2	59 (39–81)	300	VA	HP
Wensing BM	2006	Netherlands	P	NSB	30	15/15	60 (32–84)	250	VA	HP
Yamaga E	2018	Japan	R	PB	205	125/80	59.7	3.7 MBq/kg	VA	HP
Zhang H	2018	Canada	R	LB	32	NR	58.1	NR	VA	HP

Analysis: LB, Neck Level based; PB, Patient based; NSB, Neck side based.
Not reported.
Study design; R, Retrospective: P, Prospective.
VA; Visual analysis.
HP; Histopathology.

low accuracy for confirmation of the absence of cervical LN metastasis and relatively high rate of false positives [7]. F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is used to detect cervical LN metastasis in HNSCC patients more accurately than CT and MRI [8,9]. Several previous studies have been published promising role of F-18 FDG PET for the evaluation of cN0 oral cancer patients [10,11]. However, some other studies reported the limited role of F-18 FDG PET/CT for detection of LN metastasis in cN0 cancer patients [12,13].

The purpose of our study is to meta-analyze the published data on the diagnostic accuracy of F-18 FDG PET or PET/CT for the detection of LN metastasis in cN0 HNSCC patients, in order to provide more evidence-based data and to address further studies in the detection of cervical LN metastasis in cN0 HNSCC patients.

2. Methods

2.1. Data sources and search strategy

We conducted electronic English-language literature searches of PubMed and Embase database from the earliest available date of indexing through April 30, 2018. We also hand-searched the reference lists of identified publications for additional studies. We used a search algorithm based on a combination of terms: (1) “PET” OR “positron emission tomography” OR “positron emission tomography/computed tomography” OR “PET/CT” “positron emission tomography-computed tomography” OR “PET-CT”; OR “FDG” and (2) “Head and Neck Neoplasms” OR “Head and neck cancer” and (3) “Lymph node”.

2.2. Study selection

The inclusion criteria for relevant studies were as follows: F-18 FDG PET or PET/CT scan had been used to detect cervical LN metastasis in cN0 HNSCC patients; sufficient data to reassess sensitivity and specificity of F-18 FDG PET or PET/CT scan had been used to detect cervical LN metastasis in cN0 HNSCC patients or absolute numbers of true positive, true negative, false positive, and false negative data had been presented; and no data overlap.

The duplicated publications were excluded, as were publications such as review articles, case reports, conference papers, and letters, which do not contain the original data. Two researchers independently reviewed titles and abstracts of the retrieved articles, applying the above-mentioned selection criteria. Articles were rejected if clearly ineligible. The same researchers independently evaluated the full-text of the included articles to determine their eligibility for inclusion of the current review.

2.3. Data extraction and quality assessment

Information about basic study (authors, year of publication, and country of origin), study design (prospective or retrospective), patients' characteristics and technical aspects were collected.

Each study was analyzed to retrieve the number of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) findings of F-18 FDG PET or PET/CT scan had been used to detect cervical LN metastasis in cN0 HNSCC patients, according to the reference standard. Only studies providing such complete information were finally included in the meta-analysis.

The overall quality of the included studies in this review was critically appraised by 2 authors independently, based on 15-item modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS2) [14]. Discrepancies between the researchers were resolved by discussion.

2.4. Data synthesis and analysis

All data from each eligible study were extracted. The primary

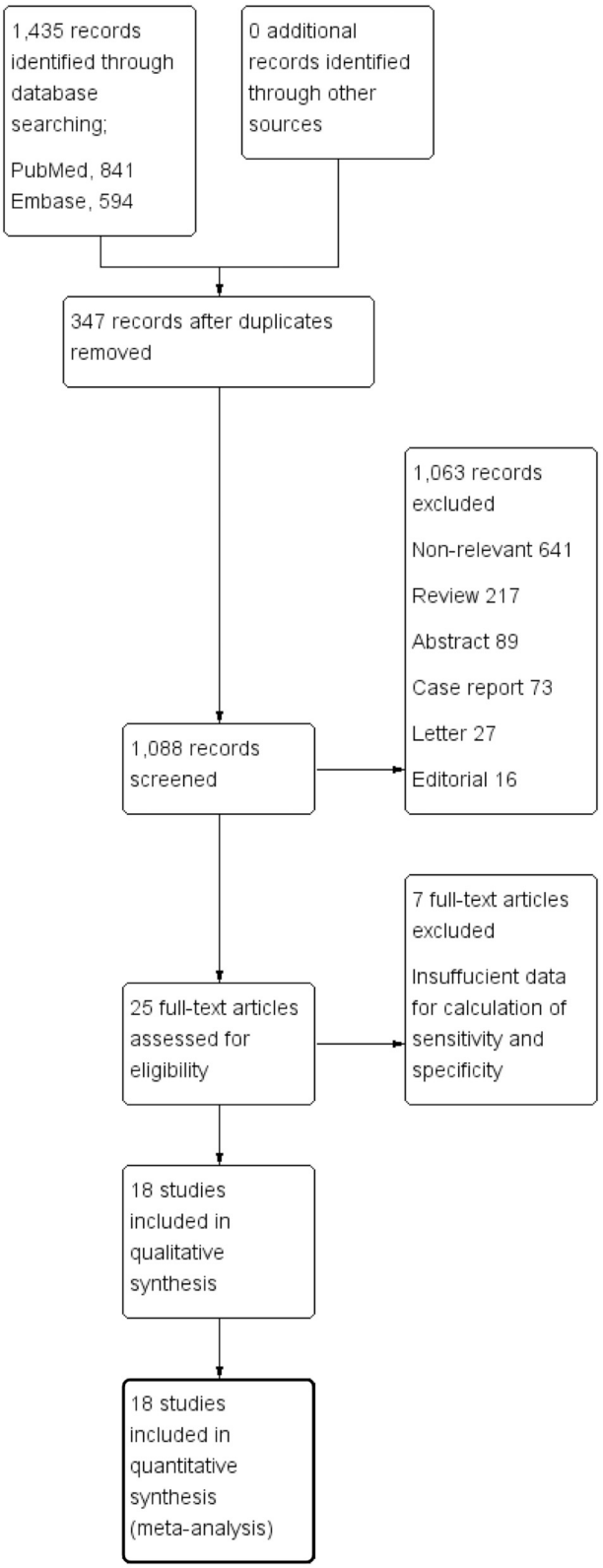

Fig. 1. Flow chart of the search for eligible studies on the diagnostic performance of F-18 FDG PET or PET/CT for the detection of LN metastasis in cN0 HNSCC patients.

objective was to estimate the sensitivity and specificity, and the positive and negative likelihood ratios (LR+ and LR−, respectively) with 95% confidence intervals (CIs), and diagnostic odds ratios (DORs) with 95% confidence intervals (CIs). A DOR can be calculated as the ratio of the

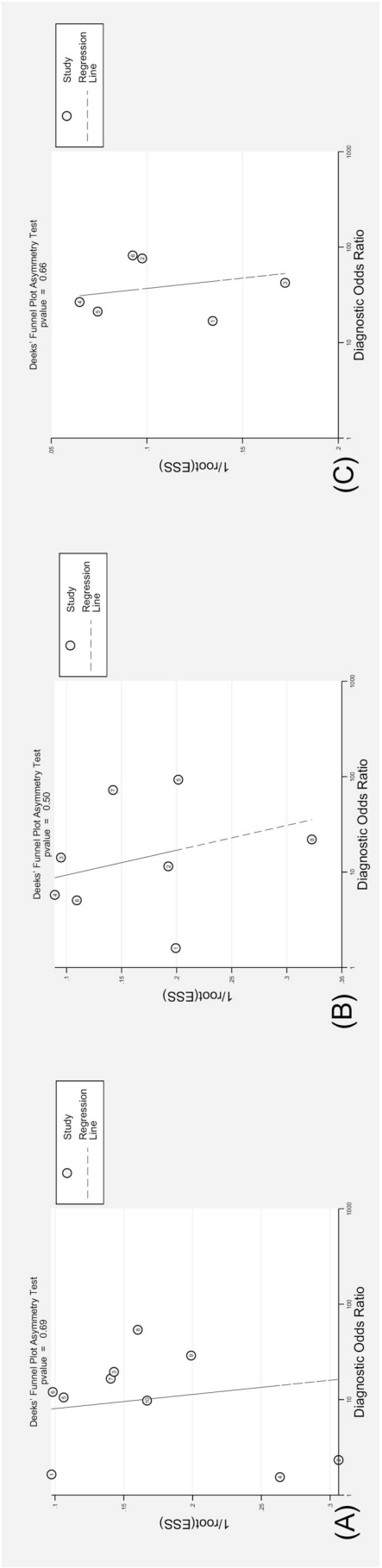

Fig. 2. Results of Deeks's funnel plot of asymmetry test for publication bias. Non-significant slope indicates that no significant bias was found. ESS; Effective sample size. (A) Patient based analysis, (B) Neck side based analysis, (C) Level based analysis.

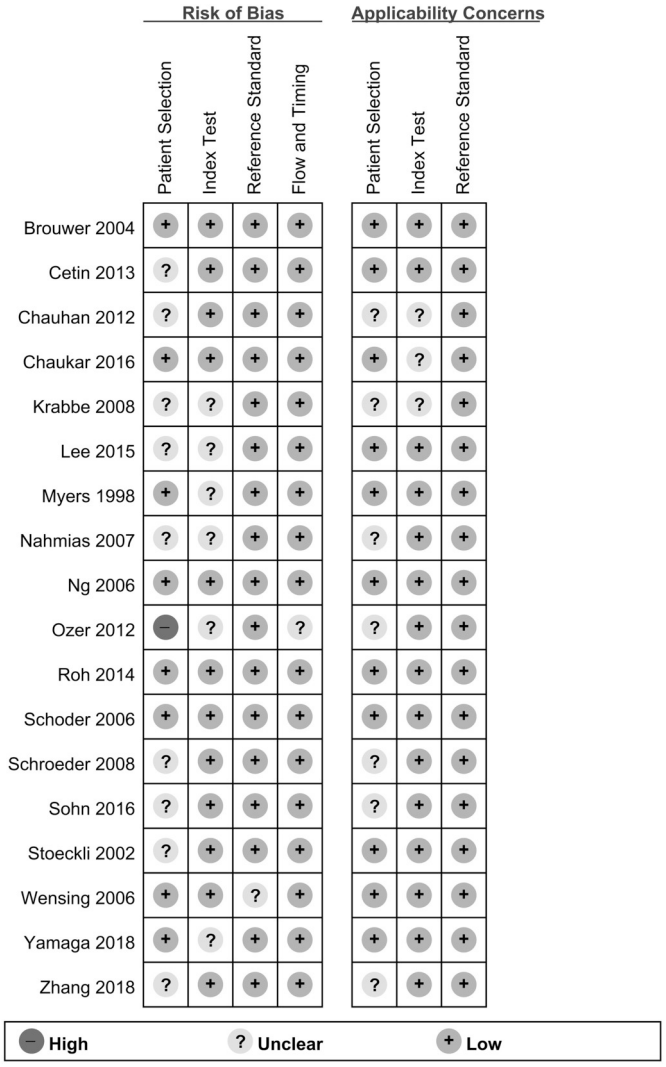

Fig. 3. Risk of bias and applicability concerns summary.

odds of positivity in a disease state relative to the odds of positivity in the non-disease state, with higher values indicating better discriminatory test performance [15]. Between-study statistical heterogeneity was assessed using I^2 and the Cochrane Q test on the basis of the random-effects analysis [16]. Publication bias was examined using the effective sample size funnel plot and associated regression test of asymmetry described by Deeks and colleagues [17]. We used the bivariate random-effects model for analysis and pooling of the diagnostic performance measures across studies, as well as comparisons between different index tests [18,19]. The bivariate model estimates pairs of logit transformed sensitivity and specificity from studies, incorporating the correlation that might exist between sensitivity and specificity. Each data point of the summary receiver operator characteristic (SROC) graph comes from an individual study; then, the SROC curve is formed based on these points to form a smooth curve to reveal pooled accuracy [20]. When statistical heterogeneity was substantial, we performed meta-regression to identify potential sources of bias [21]. The clinical or patient-relevant utility of a diagnostic test is evaluated using the likelihood ratios to calculate post-test probability (PTP) based on Bayes' theorem as follows: Pretest Probability = Prevalence of target condition PTP = LR × pretest probability / [(1 − pretest probability) × (1 − LR)] [22]. Two-sided $p \leq 0.05$ was considered statistically significant. Statistical analyses were performed with commercial software programs (STATA, version 13.1; StataCorp LP).

3. Results

3.1. Literature search and selection of studies

After the comprehensive computerized search was performed and references lists were extensively cross-checked, our research yielded 1435 records, of which 347 records of duplicated abstracts were excluded after reviewing the title and abstract. Also, non-relevant 641 studies, 73 case reports, 89 conference abstracts, 27 letters, 16 editorials, and 217 review articles were excluded. Remaining 25 full text articles were assessed for eligibility and 7 articles were excluded due to insufficient data for the calculation of sensitivity and specificity of F-18 FDG PET or PET/CT for the detection of cervical LN metastasis in cN0 HNSCC patients. Finally, 18 studies were selected and were eligible for the systematic review and meta-analysis and no additional studies were found screening the references of these articles [23–40]. The characteristics of the included studies are presented in Table 1. The detailed procedure of study selection in the current meta-analysis is shown in Fig. 1.

3.2. Study description, quality, publication bias

We conducted all analyses based on per-patient, per-neck side based, and per-level based data analysis. Among those 18 studies included in the current review, seven studies conducted patient based analysis of F-18 FDG PET or PET/CT for the detection of cervical LN metastasis in cN0 HNSCC patients [23,24,27,30,35,37,39]. Six studies conducted patient based analysis [23,25,26,29,32,38]. Three studies performed both of patient and level based analysis of F-18 FDG PET or PET/CT [28,31,36]. One study used neck side and level based analysis [34]. Only one study performed all of the patient based, neck side based and level based analysis of F-18 FDG PET or PET/CT for the detection of cervical LN metastasis in cN0 HNSCC patients [33]. Of all 18 studies, 6 studies [25,26,31,33,34,38] enrolled patients prospectively and 12 studies [23,24,27–30,32,35–37,39,40] performed retrospective analysis. There was a total of 1044 patients in the included studies, and the age ranged from 21 to 85 years. A total 621 patients were male, and 250 patients were female. Four studies did not report the number of male and female patients in their population [23,29,32,40]. All studies used visual interpretation criteria for F-18 FDG PET or PET/CT images. The principal characteristics of the 18 studies included in the meta-analysis are included in Table 1. To assess a possible publication bias, Deeks's funnel plot asymmetry tests were designed. The non-significant slope indicates that no significant bias was found (Fig. 2).

3.3. Methodological quality assessment

Fig. 3 shows the risk of bias and applicability concerns summary of the included studies and overall, the quality of the included studies was deemed satisfactory.

3.4. Diagnostic accuracy of F-18 FDG PET or PET/CT for the detection of cervical LN metastasis

The diagnostic performance results of F-18 FDG PET or PET/CT for the detection of cervical LN metastasis in cN0 HNSCC patients in the 18 included studies in the meta-analysis are presented in Table 2.

3.4.1. Patient-based analysis

The pooled sensitivity for F-18 FDG PET or PET/CT for the detection of cervical LN metastasis was 0.58 (95% CI; 0.42–0.72) with heterogeneity (I^2 = 72.2, 95% CI; 54.4–89.9, p = 0.00) and a pooled specificity of 0.87 (95% CI; 0.79–0.92) without heterogeneity (I^2 = 69.8, 95% CI; 50.1–89.5, p = 0.00). The pooled positive predictive value was 0.62 (95% CI; 0.55–0.69) and pooled negative predictive value was 0.83 (95% CI; 0.79–0.86). Likelihood ratio (LR) syntheses gave an

Table 2
Diagnostic performance of F-18 FDG PET or PET/CT for the detection of lymph node metastasis in clinically node negative head and neck cancer patients.

Authors, year	Test results, number of patients or lesions				Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
	True positive	False positive	False negative	True negative			(95% CI)	(95% CI)
Patient based analysis								
Cetin B, 2013	16	6	3	11	0.84 (0.60–0.97)	0.65 (0.38–0.86)	0.73 (0.49–0.88)	0.79 (0.49–0.94)
Krabbe CA, 2008	4	1	4	29	0.50 (0.16–0.84)	0.97 (0.83–1.00)	0.80 (0.29–0.99)	0.88 (0.71–0.96)
Lee HJ, 2015	15	1	5	18	0.75 (0.51–0.91)	0.95 (0.74–1.00)	0.94 (0.68–0.99)	0.78 (0.56–0.92)
Nahmias C, 2007	15	7	4	31	0.79 (0.54–0.94)	0.82 (0.66–0.92)	0.68 (0.45–0.82)	0.32 (0.15–0.55)
Ng SH, 2006	18	8	17	91	0.51 (0.34–0.69)	0.92 (0.85–0.96)	0.69 (0.48–0.85)	0.31 (0.15–0.52)
Roh JL, 2014	27	10	11	43	0.71 (0.54–0.85)	0.81 (0.68–0.91)	0.73 (0.56–0.86)	0.79 (0.66–0.89)
Schroeder U, 2008	0	0	5	8	0.00 (0.00–0.52)	1.00 (0.63–1.00)	NA	NA
Sohn B, 2016	16	2	9	22	0.64 (0.43–0.82)	0.92 (0.73–0.99)	0.89 (0.64–0.98)	0.71 (0.52–0.85)
Stoeckli SJ, 2002	1	1	3	7	0.25 (0.01–0.81)	0.88 (0.47–1.00)	0.50 (0.02–0.97)	0.70 (0.35–0.92)
Yamaga E, 2018	10	39	21	135	0.32 (0.17–0.51)	0.78 (0.71–0.84)	0.20 (0.11–0.35)	0.87 (0.79–0.91)
Combined	122	75	82	395	0.58 (0.42–0.72)	0.87 (0.79–0.92)	0.62 (0.55–0.69)	0.83 (0.79–0.86)
Neck side based analysis								
Brouwer J, 2004	2	1	1	11	0.67 (0.09–0.99)	0.92 (0.62–1.00)	0.67 (0.13–0.98)	0.92 (0.59–0.99)
Chauhan A, 2012	15	1	6	29	0.71 (0.48–0.89)	0.97 (0.83–1.00)	0.94 (0.68–0.99)	0.83 (0.66–0.93)
Chaukar D, 2014	30	22	7	26	0.81 (0.65–0.92)	0.54 (0.39–0.69)	0.58 (0.43–0.71)	0.79 (0.61–0.90)
Myers LL, 1998	7	0	2	15	0.78 (0.40–0.97)	1.00 (0.78–1.00)	1.00 (0.56–1.00)	0.88 (0.62–0.98)
Ozer E, 2012	26	18	20	80	0.57 (0.41–0.71)	0.82 (0.73–0.89)	0.59 (0.43–0.73)	0.80 (0.71–0.87)
Roh JL, 2014	31	12	12	66	0.72 (0.56–0.85)	0.85 (0.75–0.92)	0.72 (0.56–0.84)	0.85 (0.74–0.91)
Schöder H, 2006	6	4	3	23	0.67 (0.30–0.93)	0.85 (0.66–0.96)	0.60 (0.27–0.86)	0.88 (0.69–0.97)
Wensing BM, 2006	3	5	6	16	0.33 (0.07–0.70)	0.76 (0.53–0.92)	0.38 (0.10–0.74)	0.73 (0.49–0.88)
Combined	120	63	57	266	0.67 (0.58–0.76)	0.85 (0.74–0.92)	0.68 (0.60–0.75)	0.81 (0.76–0.85)
Level based analysis								
Lee HJ, 2015	23	4	12	171	0.66 (0.48–0.81)	0.98 (0.94–0.99)	0.85 (0.65–0.95)	0.93 (0.86–0.96)
Ng SH, 2006	21	13	30	393	0.41 (0.28–0.56)	0.97 (0.95–0.98)	0.62 (0.44–0.77)	0.93 (0.89–0.95)
Roh JL, 2014	48	30	22	366	0.69 (0.56–0.79)	0.92 (0.89–0.95)	0.62 (0.49–0.72)	0.94 (0.91–0.96)
Schöder H, 2006	6	6	3	127	0.67 (0.30–0.93)	0.95 (0.90–0.98)	0.50 (0.22–0.78)	0.98 (0.93–0.99)
Sohn B, 2016	18	2	15	127	0.55 (0.36–0.72)	0.98 (0.95–1.00)	0.90 (0.67–0.98)	0.89 (0.83–0.94)
Zhang H, 2018	3	20	11	1237	0.21 (0.05–0.51)	0.98 (0.98–0.99)	0.13 (0.03–0.35)	0.99 (0.98–0.99)
Combined	119	75	93	2421	0.53 (0.40–0.65)	0.97 (0.95–0.98)	0.61 (0.54–0.68)	0.96 (0.95–0.97)

CI; Confidence interval.
PPV; Positive predictive value.
NPV; Negative predictive value.
NA; Not available.

overall positive likelihood ratio (LR+) of 4.5 (95% CI; 2.7–7.5) and negative likelihood ratio (LR−) of 0.49 (95% CI; 0.34–0.69). The pooled DOR was 9 (95% CI; 4–19). The Fig. 4A shows hierarchical summary receiver operating characteristic (ROC) curve and indicates that the areas under the curve was 0.84 (95% CI; 0.81–0.87).

3.4.2. Neck side-based analysis

The pooled sensitivity was 0.67 (95% CI; 0.58–0.76) without heterogeneity (I^2 = 41.7, 95% CI; 0.0–89.3, p = 0.10) and a pooled specificity of 0.85 (95% CI; 0.74–0.92) with heterogeneity (I^2 = 79.8, 95% CI; 66.5–93.2, p = 0.00). The pooled positive predictive value was 0.68 (95% CI; 0.60–0.75) and pooled negative predictive value was 0.81 (95% CI; 0.76–0.85). Likelihood ratio (LR) syntheses gave an overall positive likelihood ratio (LR+) of 4.5 (95% CI; 2.5–8.4) and negative likelihood ratio (LR−) of 0.38 (95% CI; 0.29–0.51). The pooled DOR was 12 (95% CI; 5–26). The Fig. 4B shows hierarchical summary receiver operating characteristic (ROC) curve and indicates that the areas under the curve was 0.78 (95% CI; 0.74–0.81).

3.4.3. Level-based analysis

The pooled sensitivity was 0.53 (95% CI; 0.40–0.65) with heterogeneity (I^2 = 72.4, 95% CI; 49.3–95.4, p = 0.00) and a pooled specificity of 0.97 (95% CI; 0.95–0.98) with heterogeneity (I^2 = 86.7, 95% CI; 77.5–95.9, p = 0.00). The pooled positive predictive value was 0.61 (95% CI; 0.54–0.68) and pooled negative predictive value was 0.96 (95% CI; 0.95–0.97). Likelihood ratio (LR) syntheses gave an overall positive likelihood ratio (LR+) of 15.8 (95% CI; 11.0–22.6) and negative likelihood ratio (LR−) of 0.49 (95% CI; 0.38–0.63). The pooled DOR was 32 (95% CI; 21–49). The Fig. 4C shows hierarchical summary receiver operating characteristic (ROC) curve and indicates that the areas under the curve was 0.92 (95% CI; 0.89–0.94).

3.5. Heterogeneity evaluation and meta-regression analysis

Between-study heterogeneity was present for sensitivity and specificity among studies of F-18 FDG PET or PET/CT for the detection of cervical LN metastasis in cN0 HNSCC patients. A meta-regression analysis was performed to explore the possible sources of heterogeneity in the studies of F-18 FDG PET or PET/CT for the detection of cervical LN metastasis in cN0 HNSCC patients. Meta-regression showed that no definite variable was the source of heterogeneity in the current meta-analysis (Table 3).

3.6. Positive and negative post-test probability

The positive and negative post-test probability was generated based on Bayesian theory, and collected data were tabulated for 10%, 20%, and 30% pre-test probabilities of cN0 HNSCC according to the analytic method (Table 4). With pre-test cervical LN metastasis set at 10%, 20% and 30%, the post-test positive cervical LN metastasis probabilities were 33%, 53% and 66% for patient based analysis; 34%, 53% and 66% for neck side based analysis, respectively. The negative cervical LN metastasis probabilities were 5%, 11% and 17% for patient based analysis; 4%, 9% and 14% for neck side based analysis, respectively (Table 4). Fig. 5 shows the positive and negative post-test probability for level based analysis. The post-test positive cervical LN metastasis probabilities were 64%, 80% and 87%; negative cervical LN metastasis probabilities were 5%, 11% and 17% for level based analysis.

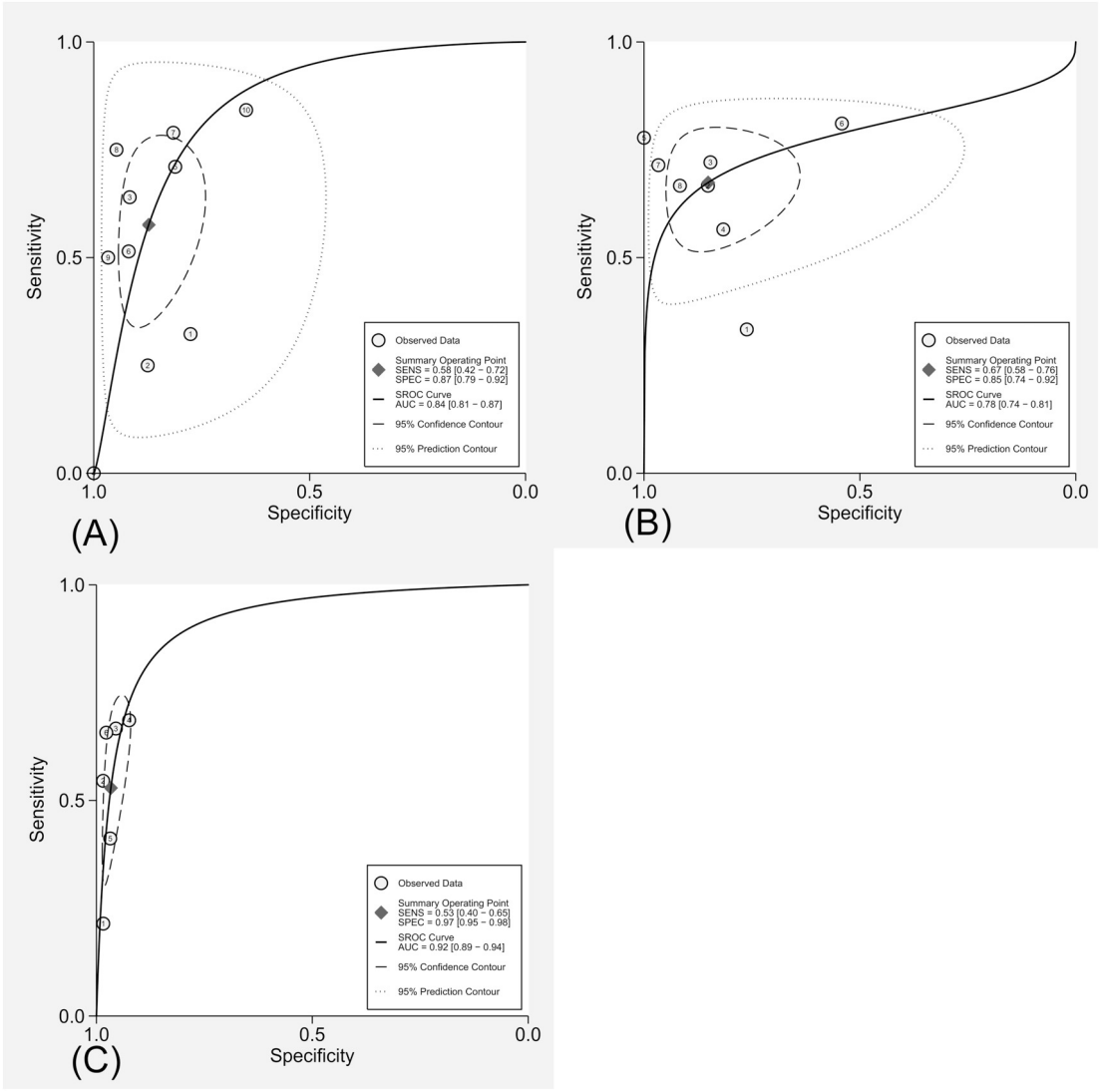

Fig. 4. Hierarchical summary receiver operating characteristic (HSROC) curves of F-18 FDG PET or PET/CT for the detection of LN metastasis in cN0 HNSCC patients. (A) Patient based analysis, (B) Neck side based analysis, (C) Level based analysis.

Table 3
Effects of moderators.

Variables	Coefficient[a]	SE	DOR	95% CI of DOR		p**
Patient based analysis						
Ethnicity (Caucasian vs Asian)	0.032	1.0652	1.03	0.08	13.99	0.9768
Study design (prospective vs retrospective)	0.160	0.9874	1.17	0.10	13.14	0.8768
Neck side based analysis						
Ethnicity (Caucasian vs Asian)	−0.137	0.9909	0.87	0.07	11.14	0.8955
Study design (prospective vs retrospective)	−0.389	1.0353	0.68	0.05	9.71	0.7228
Level based analysis						
Ethnicity (Caucasian vs Asian)	−0.517	0.6020	0.60	0.09	4.05	0.4534
Study design (prospective vs retrospective)	−0.750	0.4881	0.47	0.10	2.23	0.2221

Ethnicity (0, Asian vs 1, Caucasian); Study design (1, Prospective vs 0, Retrospective).
DOR; Diagnostic odds ratio.
SE; Standard error.
CI; Confidence interval.
[a] Regression coefficient.
** p-Value of random effect meta-regression using maximum likelihood estimation (ML) between study variances and the weighted least squares of study size for regression model estimation.

Table 4
The positive and negative predictive value of lymph node metastasis following F-18 FDG PET or PET/CT imaging among various baseline possibilities of cervical lymph node metastasis.

Analytic method	Baseline probability of cervical LN metastasis	PPV[a]	NPV[b]
Patient based analysis	10%	33%	5%
	20%	53%	11%
	30%	66%	17%
Neck side based analysis	10%	34%	4%
	20%	53%	9%
	30%	66%	14%

PPV; Positive predictive value.
NPV; Negative predictive value.
[a] Probability of cervical LN metastasis following a positive F-18 FDG PET or PET/CT imaging result.
[b] Probability of cervical LN metastasis following a negative F-18 FDG PET or PET/CT imaging result.

4. Discussion

In patients with cN0 HNSCC patients, treatment options have been determined by considering the probability of cervical LN metastasis. It is generally accepted that a watchful waiting should be considered when the risk of occult cervical LN metastases is estimated to be 20% or less [41]. If the risk of occult cervical LN metastasis is thought to be > 15–20%, elective neck treatment such as selective neck dissection or irradiation should be considered as a standard treatment [41,42]. Neck dissection is too morbid to be used as a staging tool in patients with cN0 HNSCC patients. Also, because of the high morbidity and the cost of the procedure, optimal diagnostic tools should be used to improve the preoperative assessment of the cervical LN involvement to avoid unnecessary operations and to detect patients who would have the greatest benefit from an elective neck dissection. Therefore, if preoperative imaging studies could predict the risk of cervical nodal metastasis with satisfactory sensitivity, patients without nodal metastasis could possibly avoid these procedure.

The current meta-analysis showed the low sensitivity and moderate of F-18 FDG PET or PET/CT for the detection of cervical LN metastasis in cN0 HNSCC patients by both of patient based and neck side based analysis. However, level based analysis of F-18 FDG PET or PET/CT demonstrated high specificity of 97% (95% CI; 95%–98%) and high NPV of 96% (95% CI; 95%–97%). The high specificity and NPV of the current study could be partially explained by the relatively low rate of occult cervical LN metastasis of the included 18 studies.

Anatomical imaging modalities such as US, CT and MRI, which assess primary tumors or LN metastases by size and structural changes, have improved accuracy of cervical LN staging as compared to physical palpation. However, the overall false positive or false negative rate of cervical LN metastasis by palpation has been reported as 20%–28%, while for CT ranges from 7.5% to 28% and for MRI 16% is reported [10]. Using different imaging techniques for the detection of occult cervical LN metastases, the mean reported sensitivity for CT, MRI and US guided FNAC is about 45% (range: 17–86%), with a mean specificity for CT of 89% (range: 79–97%), MRI of 86% (range 74–94%) and US guided FNAC approaching 100% [43]. Furthermore, US guided FNAC has a higher sensitivity and specificity and considered to be more cost-effective than CT and MRI. In experienced hands, the sensitivity for the N0 neck can reach 73% with a specificity of 100% [43], although others reported sensitivities ranging from 42% to 50% [44,45].

F-18 FDG PET or PET/CT have been reported to be a functional and useful imaging modality for tumor staging in different cancers [46,47]. Reports on the diagnostic value of F-18 FDG PET for the detection of occult metastatic disease have been contradictory with a reported sensitivity ranging from 0% to 100% and specificity from 92% to 100% [23,48]. Several previous studies reported high sensitivity and specificity of F-18 FDG PET or PET/CT for the detection of cervical LN metastasis in cN0 HNSCC patients [29,31,33,34]. Meyers et al. reported 78% sensitivity and 100% specificity and suggested F-18 FDG PET appears to be a promising diagnostic aid that might be applied when evaluating the NO-staged neck, especially for SCC of the oral cavity [29]. In a study with 167 patients, Roh et al. [33] demonstrated that F-18 FDG PET/CT is superior to CT/MR imaging in depicting occult cervical metastatic nodes in patients with negative neck palpation findings. The improved detection and nodal staging may promote appropriate therapeutic planning in these patients [33]. However, other

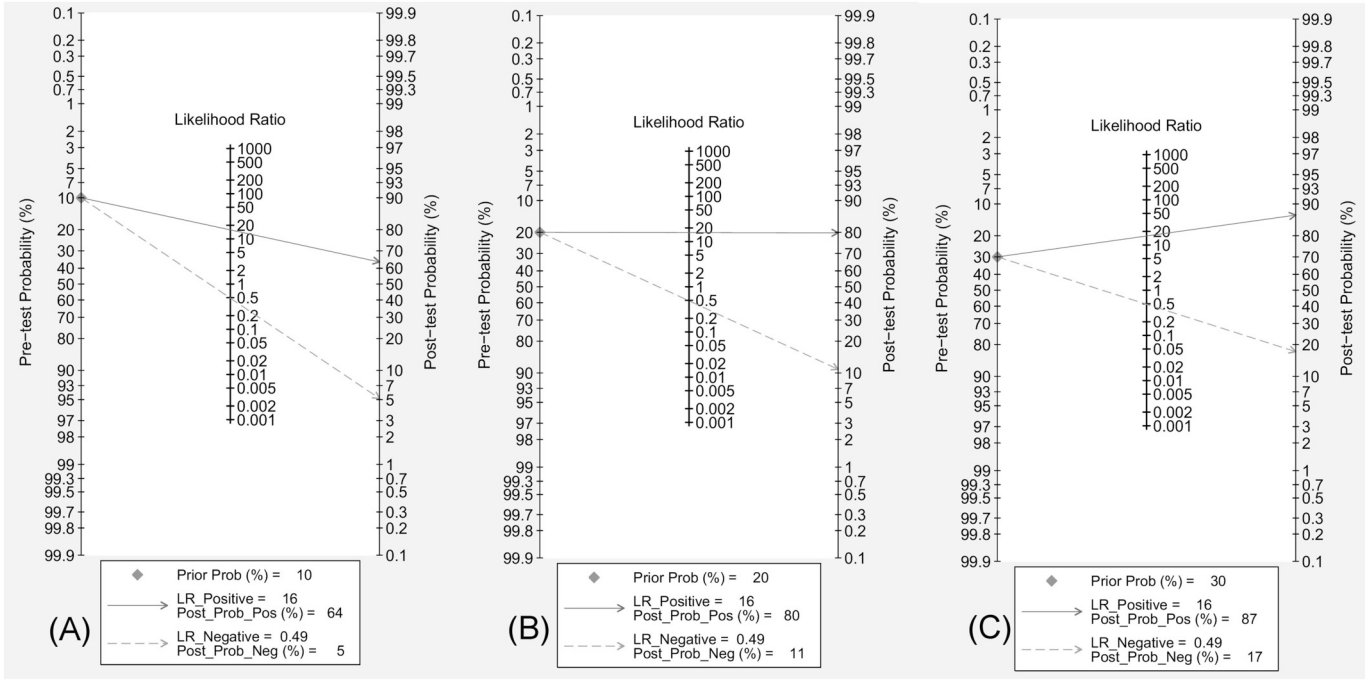

Fig. 5. The post-test positive and negative cervical LN metastasis probabilities of F-18 FDG PET or PET/CT for level based analysis.

studies reported low sensitivity and specificity of F-18 FDG PET or PET/CT for diagnosis of cervical LN metastasis [25,27,28,37,38]. Chauhan et al. reported that in N0 neck in HNSCC, though F-18 FDG PET/CT is more accurate than either US or CT in staging of the neck, it is not accurate enough to alter the current treatment paradigm [25]. Lee HJ et al. also showed that the addition of PET-CT examination to anatomic imaging involving CT and MR did not provide additional benefit for the preoperative evaluation of cervical LN metastasis in patients with hypopharyngeal SCC with non-palpable neck, yielding insufficient data to spare elective neck dissection [28]. In a study of 112 N0 patients, a recent study showed 57% sensitivity and 82% specificity [32]. They concluded that PET/CT has a much reduced rate of efficacy for the cN0 compared to the clinically positive neck and PET/CT in its current stage does not appear to offer an advantage in staging the clinically N0 neck due to high rates of false positives and negatives [32].

In the current meta-analysis, we found F-18 FDG PET or PET/CT had fair diagnostic performance in cN0 HNSCC patients with regard to post-test probability of LN metastasis. For positive imaging results, elective neck dissection should be considered because for low risk patients with pre-test probability below 30% of LN metastasis, post-test probability as high as 87% based on the level based analysis.

Recent systematic review and meta-analysis showed that F-18 FDG PET/CT has sensitivities of 66%, 50% and specificities of 87%, 86% for detecting cervical LN metastases in cN0 HNSCC patients [12,49]. Based on the 8 studies, Liao et al. reported the pooled estimates for sensitivity of 66% (95% CI; 47–80%) and the pooled estimates for specificity of 87% (95% CI; 77–93%) [12]. Another study showed that for cN0 patients, sensitivity of F-18 FDG PET was only 50% (95% CI = 37% to 63%), whereas specificity was 87% (95% CI = 76% to 93%) [49]. They concluded that although F-18 FDG PET has good diagnostic performance in the overall pretreatment evaluation of patients with HNSCC but still does not detect disease in half of the patients with metastasis and cN0 [49].

The major drawback of the current meta-analysis is that we could not perform the further analysis according to the sub-site or sub-type of tumors because most included studies did not report the diagnostic performance according to sub-site or sub-type of tumors. As seen in the updated AJCC 8th edition of staging, there are diversities in staging for the different sub-sites and sub-types of tumors due to different tumor behaviors, cervical LN metastasis patterns, and treatment options for those tumors. Therefore, it would be difficult to generalize the current results from a combined studies to any particular tumor.

The current meta-analysis showed a considerable heterogeneity of sensitivity between studies. The included studies were statistically heterogeneous in their estimates of sensitivity. This heterogeneity is likely to arise through diversity in methodological aspects between different studies and the basic differences among the patients in the included studies may have contributed to the observed heterogeneity of the results too. However, in meta-regression analysis of the current review, no definite variable in this study did not possess some sources of heterogeneity. To minimize bias in the selection of studies and in the data extraction, reviewers who were blinded to the journal, author, institution, and date of publication independently selected articles based on the inclusion criteria, and scores were assigned to study design characteristics and examination results by using a standardized form that was based on the QUADAS2 tool. Also, publication bias is a major concern in all meta-analyses as studies reporting significant findings are more likely to be published than those reporting non-significant results. We assessed the publication bias in our analysis by using funnel plots which showed no definite asymmetry.

5. Conclusion

The current meta-analysis showed the low sensitivity and moderate specificity of F-18 FDG PET/CT for the detection of cervical LN metastasis in cN0 HNSCC patients. Level based analysis of F-18 FDG PET or PET/CT has a high specificity and NPV for the detection of cervical metastatic LN detection. At present, the literature regarding the use of F-18 FDG PET or PET/CT for this purpose remains still limited; thus, further large multicenter studies would be necessary to substantiate the diagnostic accuracy of F-18 FDG PET or PET/CT for the detection of cervical LN metastasis in cN0 HNSCC patients.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Ethical approval

Institutional review board approval was not required because we only performed data analysis based on the published studies.

Informed consent

Written informed consent was not required for this study because it is a meta-analysis based on the studies that have been published.

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