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FULL PAPER

Meta-analysis of diagnostic value of ^{18}F -FDG PET or PET/CT for detecting lymph node and distant metastases in patients with nasopharyngeal carcinoma

G SHEN, MD, W ZHANG, MD, Z JIA, PhD, J LI, MD, Q WANG, MD and H DENG, MD

Department of Nuclear Medicine, West China Hospital, Sichuan University, Sichuan, China

Address correspondence to: Dr Houfu Deng
E-mail: denghfy@126.com

The authors Guohua Shen and Wenjie Zhang contributed equally to this work.

Objective: We performed this meta-analysis to comprehensively assess the diagnostic performance of positron emission tomography (PET) or PET/CT for detecting lymph node and distant metastases in patients with nasopharyngeal carcinoma (NPC).

Methods: Through a search of four English and three Chinese databases (January 1990 to June 2013), pooled estimated sensitivity, specificity and diagnostic odds ratio (DOR) were calculated based on the data extracted from the included studies. We also constructed summary receiver operating characteristic curves, with the area under the curve (AUC) and obtained the Q^* index. Heterogeneity and subgroup analysis were also performed.

Results: In total, 18 articles consisting 20 studies were included in this meta-analysis. On a per-patient basis, the

overall pooled estimates for sensitivity and specificity of PET or PET/CT in N and M staging of NPC were 0.89 [95% confidence interval (CI), 0.86–0.91] and 0.96 (95% CI, 0.95–0.96), respectively. The overall DOR, AUC and Q^* index were 162.07 (95% CI, 90.72–289.55), 0.9689 and 0.9181, respectively. Subgroup analysis showed that AUC and Q^* index were 0.9734 and 0.9255 for N staging and 0.9715 and 0.9223 for M staging, respectively.

Conclusion: The present meta-analysis showed that PET or PET/CT has excellent diagnostic performance for detecting lymph node and distant metastases in patients with NPC.

Advances in knowledge: To provide evidence to assess the role of PET or PET/CT in staging of NPC.

In Western countries, nasopharyngeal carcinoma (NPC) is a rare form of squamous cell carcinoma, with incidence rates <1 per 10^5 persons per year. However, it is a highly frequent epithelial malignancy of the head and neck in southern China and parts of Southeast Asia, with a reported annual incidence of 30–80 per 10^5 persons in endemic regions, mainly owing to Asian ancestry and infection with the Epstein–Barr virus.^{1–3} The mainstay of treatment for nasopharyngeal cancers is using 100 mg m^{-2} of cisplatin on Days 1, 22 and 43 concurrent with radiotherapy, followed by adjuvant 80 mg m^{-2} of cisplatin on Day 1 and 1000 mg m^{-2} of 5-fluorouracil on Days 1–4 for three cycles.^{4,5} It is known that stage-adapted therapy significantly improved the survival of patients with cancer.^{6,7} In this regard, conventional CT and MRI, mainly providing anatomical information, are performed to assess staging site of NPC, especially for the primary site and local-regional metastases. However, owing to the lack of functional information, these modalities are limited in

assessment of disease aggressiveness and distant metastases.⁸ Furthermore, it is difficult to diagnose residual or recurrent NPC owing to the presence of soft-tissue inflammation and oedema after radiotherapy.⁹ In addition, some small volume metastatic nodal lesions may be misinterpreted as reactive nodes when patients show reactive hyperplasia in lymph nodes.

Positron emission tomography (PET) and in particular integrated PET/CT using fluorine-18 fludeoxyglucose (^{18}F -FDG), the latter uniting metabolic function with anatomic form, are widely used techniques in the cancer staging assessment in recent years. Many studies on the staging value of PET or PET/CT for patients with NPC have been performed. For T staging of NPC, PET/CT was less sensitive than MRI, which is plausibly ascribed to the facts that early tumour invasion may have poor ^{18}F -FDG uptake owing to low tumour burden, while these anatomic areas, including the intracranial area along the cranial nerve, the

parapharyngeal space, the skull base and sphenoid sinuses, may be obscured by the spillover effect of ^{18}F -FDG PET. On the other hand, compared with MRI, partial volume and lack of consensus of optimal strategy for tumour delineation on ^{18}F -FDG PET may lead to T overstaging. MRI appeared to be superior to PET/CT in delineating primary tumour extent.¹⁰ The use of PET/CT without MRI may lead to inappropriate coverage by radiation portals or improper use of chemotherapy. PET or PET/CT did not have adequate contrast resolution to identify retropharyngeal lymph nodes that merged with adjacent primary tumour or to discriminate direct tumour invasion from metastases, which may result in incorrect N staging or improper use of chemotherapy.¹⁰ However, ^{18}F -FDG PET/CT may be more accurate than conventional work-up for the determination of neck status and identifying cervical lymph node metastasis, which could facilitate a more appropriate treatment plan, especially for portal designation.^{10–12} For those suspicious lymph nodes on conventional imaging or PET/CT, pathological examination may still be necessary. Ultrasound-guided fine-needle aspiration, allowing cytological examination of suspicious nodes as small as 2 mm in diameter, may be a minimally invasive procedure that can enable cytological examination of suspicious lymph nodes.¹³ It has good specificity and a high positive-predictive value but a poor negative-predictive value for identification of metastatic lymph nodes from NPC; furthermore, fine-needle aspiration cytology of the node frequently yields inconclusive results, and this is likely to be related to the increased fibrosis within these nodes after radiation.¹³ With regard to distant metastasis, PET/CT has an acceptable diagnostic yield and a low false-positive rate for the detection of distant malignancy and can replace conventional work-up for this aim.^{10,14,15}

To our knowledge, the results of previous studies are controversial, mainly because of different study design, selection criteria and reference standard. Thus, we performed a meta-analysis of all available studies to comprehensively assess their value in detecting lymph node and distant metastases in patients with NPC.

METHODS AND MATERIALS

Literature search and study selection

A comprehensive computer literature search of studies was performed to identify articles about the diagnostic performance of ^{18}F -FDG PET or integrated PET/CT for the detection of lymph node and distant metastases of NPC. PubMed, EMBASE, EBSCO, Web of Science databases and three Chinese databases CBM, CNKI and Wanfang, from January 1990 to June 2013, were searched for relevant articles with the combination of the following keywords: (nasopharyngeal carcinoma OR nasopharyngeal cancer) AND (PET OR positron emission tomography OR PET/CT OR FDG OR fluorodeoxyglucose), and with no language restrictions. References of selected studies were also screened for additional relevant studies.

Studies were eligible for inclusion based on the following criteria: (a) ^{18}F -FDG PET or PET/CT was used to assess tumour N and M staging of NPC. (b) Histopathological analysis and/or clinical and imaging follow-up were used as the reference standard. (c) Absolute numbers of true positive (TP), true

negative (TN), false positive (FP) and false negative (FN) could be extracted directly or calculated based on sufficient data to construct a 2×2 table. (d) There were at least ten patients involved in the included studies, and the results were based on per-patient statistics. (e) When data were presented in more than one article, the article with most details or the most recent article was chosen. Studies were excluded if data were unavailable for deriving 2×2 tables. Reviews, letters, case reports and meeting abstracts were also excluded.

Data extraction and quality assessment

Two reviewers independently extracted data, with any disagreement resolved by consensus. For each included study, information was extracted concerning basic study information (author names, year of publication, country of origin and reference standard), patient characteristics (number, gender and age), study design (prospective or retrospective) and technical aspects (modality used, radiopharmaceutical dose, time interval between injection and image acquisition). What is more, 2×2 tables were extracted from all eligible studies, including the numbers of TP, FP, FN and TN. Data extracted from publications alone is deemed adequate for the purpose of this meta-analysis without contacting the authors for more information.

The methodological quality of included studies was assessed on the basis of the quality assessment tool for diagnostic accuracy studies (QUADAS).¹⁶ The QUADAS tool included 14 items, each of which was assessed as “yes” or “no”.

Statistical analysis

In order to evaluate the diagnostic value of ^{18}F -FDG PET or PET/CT in N and M staging of NPC, we calculated the pooled estimates of sensitivity, specificity, diagnostic odds ratios (DORs) and their 95% confidence interval (CI). The likelihood ratios are metrics that combine both sensitivity and specificity in their calculation. The positive likelihood ratio (PLR) is defined as the ratio of sensitivity over (1-specificity), and the negative likelihood ratio (NLR) is defined as the ratio of (1-sensitivity) over specificity. The DOR was provided by the ratio of PLR relative to NLR, with higher values indicating better performance. In addition, summary receiver operating characteristic (SROC) curves were drawn, with the area under the curve (AUC) and Q^* index obtained. Q^* index is the best statistical method to reflect the diagnostic value, it is defined by the point where sensitivity and specificity are equal, which is the point closest to the ideal top-left corner of the SROC space.¹⁷ The degree of heterogeneity among different studies was tested using the I^2 test. When there was significant heterogeneity observed, namely the I^2 value was $>50\%$, a random-effect model was applied, otherwise a fixed-effect model was used.¹⁸ All analyses were performed using Meta-Disc v. 1.4 (XI Cochrane Colloquium, Barcelona, Spain).

RESULTS

Literature search and study design characteristics

Our search strategy identified a total of 655 potentially relevant articles. After reviewing the title and abstract, we excluded 556 obviously irrelevant articles. For the remaining 99 articles, we read full texts, and 18 articles^{10,12,14,15,19–32} consisting 20 studies fulfilled all inclusion criteria and were included for data analysis.

The main reasons for exclusion were as follows: (1) the aim/topic of the articles was not to reveal the diagnostic value of PET or PET for N and M staging of NPC ($n = 344$); (2) case reports, reviews or meeting abstracts, which did not report enough data ($n = 212$); (3) data not available or sufficient for calculating TP, FP, FN and TN results ($n = 45$); (4) duplicated studies ($n = 32$); and (5) data analysis based on per-lesion statistics ($n = 4$).

The detailed characteristics of included studies are summarized in Table 1. A total of 18 articles, including 20 studies and involving 2396 patients, were included in the analysis. In all studies, the results of the diagnostic performance were patient based. There were 7 studies for N staging and 13 studies for M staging. Eight articles^{10,14,15,23,25–27,32} certainly enrolled patients prospectively, and the other study designs were retrospective. Obviously, most studies were performed in Asia, especially in China. With regard to the reference standard, only one study²⁴ used histopathological analysis alone, while most studies used the combination of histopathological results and clinical follow-up or the combination of clinical follow-up and imaging findings. The histopathological results could be obtained by biopsy or surgical excision.^{10,26} In addition, some information about scanning technique is also presented in Table 1. Only four studies used PET, while all the rest used PET/CT. The amount of radiotracer was 370 Mbq, and the time interval was 45–60 min in most studies.

Quality assessment

We assessed the quality of the included studies according to the 14-item QUADAS tool, and the scores are presented in Table 2. 9 of the 14 items could be answered as “Yes” in all included studies: representative spectrum (Item 1), clear selection criteria (Item 2), acceptable reference standard (Item 3), acceptable delay between tests (Item 4), partial verification (Item 5), incorporation bias (Item 7), the index test in detail (Item 8), the reference standard in detail (Item 9) and clinical data analysis (Item 12). Only one study²⁴ reported that all patients received the same reference standard regardless of the index test result (Item 6). No study reported that the reference standard was masked to the index test result (Item 11), and the index test was masked to the reference standard (Item 10) in 12 studies.^{10,14,15,19,22,24–27,30–32} The reporting of uninterpretable results (Item 13) and explanation of withdrawals from the study (Item 14) were presented in 12 studies^{10,12,14,15,19–21,25,28,30–32} and 4 studies^{10,14,26,27}, respectively.

Summary estimates of meta-analysis

When we considered all 20 studies (2396 patients) with data on per-patient basis for N and M staging of NPC, the overall sensitivity was 0.89 (95% CI, 0.86–0.91) and the specificity was 0.96 (95% CI, 0.95–0.96). DOR syntheses yielded overall DOR of 162.07 (95% CI, 90.72–289.55) (Table 3). In SROC curves, the AUC and Q^* index were 0.9689 and 0.9181, respectively; indicating a high level of overall accuracy (Figure 1a).

For lymph node metastasis, we considered all seven studies.^{12,21–24,30,31} The pooled sensitivity, specificity and DOR of PET or PET/CT in the diagnosis of N staging were 0.90 (95% CI, 0.87–0.93), 0.92 (95% CI, 0.89–0.95) and 193.60 (95% CI,

47.27–792.89), respectively (Table 3). The AUC and Q^* index were 0.9734 and 0.9255, respectively (Figure 1b).

For M staging of NPC, 13 studies were eligible for meta-analysis.^{10,14,15,19,20,25–32} The pooled sensitivity, specificity and DOR were 0.87 (95% CI, 0.83–0.90), 0.96 (95% CI, 0.95–0.97) and 161.12 (95% CI, 96.29–269.59), respectively (Table 3). Our analysis showed that the AUC was 0.9715 and Q^* index was 0.9223 (Figure 1c).

Heterogeneity results and subgroup analysis

Table 3 showed the results of heterogeneity and subgroups analysis. The I^2 values of sensitivity, specificity and DOR for N staging were 66.7%, 75.1% and 62.0%, respectively. The corresponding values for M staging were 68.0%, 77.1% and 5.5%, respectively. These results indicated homogeneity for DOR but heterogeneity for sensitivity and specificity. Considering that the results might be influenced by the study design and scanning technique, we performed subgroup analysis based on “prospective” or “retrospective” subgroups and “PET alone” or “PET/CT” subgroups. However, there were no sufficient data for subgroup analysis of N staging in these two aspects, and only subgroup analysis for M staging was performed. The result showed that the sensitivity and DOR of the “prospective group” were significantly higher than those of the “retrospective group” ($p < 0.05$), while the specificity showed no statistical difference ($p > 0.05$). There were no significant differences found for “PET” and “PET/CT” ($p > 0.05$). In addition, on the basis of different population (newly diagnosed and recurrent primary NPC), we performed subgroup analysis for N and M staging. For N staging, the diagnostic value of “recurrent primary NPC” was significantly higher than that of the “newly diagnosed” ($p < 0.05$), while for M staging, the sensitivity and DOR of “recurrent primary NPC” were significantly higher than those of the “newly diagnosed” with lower specificity ($p < 0.05$). Furthermore, we conducted a meta-regression analysis to assess the causes of heterogeneity, including the sample size, mean age, year of publication and scanning techniques. No apparent relationships were found.

DISCUSSION

NPC is a radiosensitive head and neck malignancy prone to distant metastases. Accurate initial assessment of the primary site of NPC, nodal involvement and distant metastases are significantly important for NPC patients in the staging, treatment planning and prognosis judgment.^{25,33} Our meta-analysis showed that ^{18}F -FDG PET or PET/CT had a high level of overall accuracy (the sensitivity for 0.89 vs the specificity for 0.96) for detection of the lymph node and distant metastases.

Primary malignancies of the nasopharynx are often understaged during clinical examination. Local spread of NPC can be in the form of skull base involvement or intracranial extension. It is difficult to do a biopsy in these parts, and the judgment whether or not there is an extension of the tumour depends on clinical and imaging information. Owing to strong background tracer uptake in the brain as well as poorer image resolution, ^{18}F -FDG PET or PET/CT is not generally ideal for assessment of

Table 1. Study characteristics for selected studies

Study	Origin	Population	n	Male	Mean/median age (years)	Study design	Reference standard	Lesion invasion	PET system and technique
N staging									
Sun and Fan ²¹	China	ND (347)	347	276	45	R	HP CFU	Retropharyngeal lymph node metastasis	PET/CT: 5.5 MBq kg ⁻¹ ; 45–60 min
Zhang et al ¹²	China	ND (116)	116	92	15–73	R	IF CFU 6–18 mo	Lymph node metastasis	PET/CT: 296–440 MBq; 45–60 min
Shen et al ²²	China	RP (43)	43	30	35–79	R	HP CFU 6–48 mo	Lymph node metastasis	PET/CT: 370–555 MBq; 40–60 min
Lin et al ²³	China	ND (62)	62	48	43	P	IF CFU >6 mo	Retropharyngeal lymph node metastasis	PET/CT: 5.55 MBq kg ⁻¹ ; 40–60 min
Hu et al ²⁴	China	ND (30)	30	17	45	R	HP	Small cervical lymph nodes	PET/CT: 5.55 MBq kg ⁻¹ ; 45–60 min
Chen et al ³¹	Taiwan	ND (20); RP (50)	70	52	46.3 for 20; 50.7 for 50	R	IF CFU >6 mo	Regional nodes	PET/CT: 370 MBq; 60 ± 10 min
Comoretto et al ³⁰	Italy	RP (63)	63	44	52	R	HP CFU >6 mo	Regional nodes	PET/CT: 350–400 MBq; 60 min
M staging									
Zhang et al ¹⁹	China	ND (257)	257	201	45	R	HP CFU 36–60 mo	Distant metastases	PET/CT: 296–440 MBq; 45–60 min
Xu et al ²⁰	China	RP (41)	41	26	53.5 ± 12.5	R	IF CFU	Distant metastases	PET/CT: 0.15 mCi kg ⁻¹ ; 40–60 min
Li et al ²⁹	China	ND (22); RP (53)	75	33	56.7	R	HP CFU	Distant metastases	PET/CT: 4.81–7.40 MBq/kg; 45–60 min
Yen et al ²⁵	Taiwan	ND (118); RP (22)	140	97	49.4 ± 12.4	P	HP CFU 3–6 mo	Distant metastases	PET: 370 MBq; unclear
Ng et al ¹⁰	Taiwan	ND (150)	150	111	48.17	P	HP CFU	Distant metastases	PET/CT: 370 MBq; 50–70 min
Ng et al ¹⁴	Taiwan	ND (111)	111	84	48.9	P	HP CFU >12 mo	Distant metastases	PET/CT: 370 MBq; 50–70 min
Liu et al ²⁶	Taiwan	ND (300)	300	210	50	P	HP CFU	Distant metastases	PET: 370 MBq; 40 min
Liu et al ²⁷	Taiwan	ND (202)	202	147	49.6	P	HP CFU	Bone metastases	PET: 370 MBq; 40 min
Lin et al ²⁸	China	ND (216)	216	168	45.0 ± 11.2	R	HP CFU	Distant metastases	PET/CT: 296–440 MBq
Chen et al ³¹	Taiwan	ND (20); RP (50)	70	52	46.3 for 20; 50.7 for 50	R	IF CFU >6 mo	Distant metastases	PET/CT: 370 MBq; 60 ± 10 min

(Continued)

Table 1. (Continued)

Study	Origin	Population	n	Male	Mean/median age (years)	Study design	Reference standard	Lesion invasion	PET system and technique
Chang et al ³²	Taiwan	ND (85); RP (10)	95	66	47	P	HP CFU >6 mo	Distant metastases	PET: 370 MBq; 40 min
Chua et al ¹⁵	Singapore	ND (78)	78	60	50	P	HP CFU 6 mo	Distant metastases	PET/CT: 370 MBq; 60 min
Comoretto et al ³⁰	Italy	RP (63)	63	44	52	R	HP CFU >6 mo	Distant metastases	PET/CT: 350–400 MBq; 60 min

CFU, clinical follow-up; HP, histopathology; IF, imaging findings; MBq, mega Becquerel; mo, month; ND, newly diagnosed; P, prospective; PET, positron emission tomography; R, retrospective; RP, recurrent primary nasopharyngeal carcinoma.

intracranial disease or local lesions, while MRI is accepted to be better for assessment of both the local extent and intracranial extension. In addition, the specificity of PET or PET/CT was relatively low because of the radiation response after treatment. MR demonstrated a trend towards higher accuracy than did FDG PET/CT in depicting the primary tumour site of NPC.³⁰ Even though PET/CT can demonstrate obvious primary sites, local lesions or intracranial extension of NPC in some cases if the primary tumour is significantly more hypermetabolic than its surroundings, its technical limitations, availability and relatively higher cost do not warrant it replacing MRI as the modality of choice for local staging.³⁴

Among patients with NPC, the pattern of regional lymph node metastasis is a predictor of distant failure and can significantly influence radiotherapy planning. ¹⁸F-FDG PET/CT was found to be more globally effective than conventional work-up (CT and MRI) for detecting cervical lymph nodal metastases.^{27,35,36} The role of PET/CT in detecting cervical lymph node metastasis in patients with NPC at initial diagnosis has been reported previously. In the study by Comoretto et al³⁰ evaluating 63 patients with NPC with PET/CT and MRI, PET/CT was found to be more effective than MRI (accuracy, 96.8% vs 90.5%) in evaluating regional lymph nodes. In two other studies, researchers also reported a higher accuracy of PET than MRI for M staging.^{11,12} In addition, we should recognize the fact that PET/CT did not have adequate contrast resolution to identify those retropharyngeal nodes that merged with adjacent primary tumours or to discriminate direct tumour invasion from retropharyngeal metastasis.¹⁰ The presence of distant metastases is an important prognostic factor in patients with NPC, and patients with NPC still remain at significant risk for distant failure and second primary cancers after treatment. Thus, a fast, accurate, reliable diagnostic work-up is of utmost importance. Whole-body ¹⁸F-FDG PET or PET/CT has been shown to be useful for detecting distant metastases in patients with NPC. Ng et al¹⁰ found that PET/CT was more sensitive and accurate than conventional imaging (sensitivity, 81.3% vs 25.0%; accuracy, 94.6% vs 88.3%) in M staging of NPC. In the study by Liu et al,²⁶ PET/CT also had better overall diagnostic performance than did conventional work-up (94.0% vs 83.7% in accuracy). Similar results were also demonstrated in some other studies.^{15,25,32} In addition, bone metastasis occurs frequently in patients with NPC, and it is necessary to evaluate PET/CT for detecting bone metastasis at initial staging. Liu et al²⁷ reported that 30 (15%) of 202 eligible patients were found to have bone metastasis. PET/CT was more effective than skeletal scintigraphy in both patient-based analysis (94.6% vs 88.6% accuracy) and region-based analysis at the spine (93.1% vs 88.1% accuracy). In the study of Chua et al,¹⁵ they compared the efficacy of four modalities (conventional work-up, combined CT and skeletal scintigraphy, PET and PET/CT) to assess distant metastasis and suggested that PET/CT was the most sensitive, specific and accurate modality for M staging of NPC.

In our meta-analysis, the subgroup analysis for the patient population showed that PET or PET/CT was a valuable imaging tool for the initial staging of newly diagnosed group and restaging of recurrent primary NPC group. The diagnostic

Table 2. Evaluation of quality of included studies using quality assessment tool for diagnostic accuracy studies (QUADAS) tool

Study	Item														Total score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Chang et al ³²	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	11
Chen et al ³¹	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	11
Chua et al ¹⁵	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	11
Comoretto et al ³⁰	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	11
Li et al ²⁹	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y	N	N	9
Lin et al ²⁸	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y	Y	N	10
Liu et al ²⁶	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	11
Liu et al ²⁷	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	11
Ng et al ¹⁴	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	12
Ng et al ¹⁴	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	12
Yen et al ²⁵	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	11
Hu et al ²⁴	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	11
Lin et al ²³	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y	N	N	9
Shen et al ²²	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	N	10
Sun and Fan ²¹	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y	Y	N	10
Xu et al ²⁰	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y	Y	N	10
Zhang et al ¹²	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y	Y	N	10
Zhang et al ¹⁹	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	12

N, no or unclear = 0 score; Y, yes = 1 score.

performance of PET or PET/CT was higher in the latter group, for the main reason that up to 30% have distant recurrence after primary definitive radiotherapy,³⁷ and PET or PET/CT was recommended for the staging and assessment of recurrence in patients with NPC.³⁸ In addition, not all patients underwent PET or PET/CT scan for initial staging. With regard to other subgroup analyses for M staging, integrated PET/CT, combining functional imaging of PET and anatomic imaging of CT, compensated for the poor spatial resolution of PET alone, which may restrict its use for assessing distant metastasis. Actually, most centres now have integrated PET/CT systems, and with the new crystals and techniques widely used, PET/CT has a better spatial resolution (transverse resolution: 4.4–4.9 mm; axial resolution: 4.5–5.6 mm in general), to be more accurate, for lesion localization and characterization than PET and CT alone.^{39,40} However, our analysis was unable to identify if ¹⁸F-FDG-PET/CT is better than ¹⁸F-FDG-PET alone ($p > 0.05$). Upon review of literature, two studies also revealed no statistically significant difference between PET/CT and PET alone for detecting distant malignancies.^{15,31} Limited evidence supports the notion that integrated PET/CT may obviously improve diagnostic accuracy over that achieved with PET alone. Moreover, the pooled estimates of the “retrospective subgroup” were higher than those of the “prospective subgroup”. The retrospective nature of studies can be considered a limitation because of the possibility that the imaging interpreter might have known the diagnostic outcomes of other

imaging modalities before assessing PET or PET/CT images, which may potentially lead to higher accuracy.

Besides the patient population, study design and imaging modality, several other differences in study characteristics may be sources of heterogeneity. The gold standard for lymph node and distant metastases was histological confirmation. However, this may not always be feasible. In our study, only one study used histopathological analysis alone, whereas most studies used a combination of histopathological results and clinical follow-up or imaging findings. The difference in reference standard may be a source of heterogeneity between studies. In addition, there was no standard follow-up strategy or time. This factor may have affected the accuracy of whole-body PET/CT for the detection of distant malignancies in patients with NPC. For example, the negative findings during the relatively short follow-up period may prove to be truly positive if the time of the follow-up period is long enough which potentially biased our results. Because of limited data and small sample size, we were not able to evaluate the publication bias, which was a potential source of heterogeneity.

The DOR is a single indicator of test accuracy that combines the data from sensitivity and specificity into a single number.⁴¹ It is the ratio of the odds of a positive test in a patient with disease relative to the odds of positive test in a patient without disease, which has a value that ranges from 0 to infinity, and higher values indicate better discriminatory test performance. In this

Table 3. Diagnostic accuracy of positron emission tomography (PET)/CT for overall evaluation of N and M staging in patients with nasopharyngeal carcinoma

Study	No./no.	SEN (95% CI)	I ² of SEN (%)	SPE (95% CI)	I ² of SPE (%)	DOR (95% CI)	I ² of DOR (%)	AUC	Q* index
Overall	20/2396	0.89 (0.86–0.91)	67.1	0.96 (0.95–0.96)	77.5	162.07 (90.72–289.55)	43.8	0.9689	0.9181
N staging	7/731	0.90 (0.87–0.93)	66.7	0.92 (0.89–0.95)	75.1	193.60 (47.27–792.89)	62.0	0.9734	0.9255
ND ^a	5/575	0.90 (0.86–0.93)	73.2	0.90 (0.85–0.94)	62.8	99.42 (27.16–357.97)	39.9	0.9654	0.9126
RP ^a	3/156	0.95 (0.83–0.99)	0.0	0.97 (0.92–0.99)	69.9	347.73 (32.93–3671.5)	44.3	0.9650	0.9120
M staging	13/1798	0.87 (0.83–0.90)	68.0	0.96 (0.95–0.97)	77.1	161.12 (96.29–269.59)	5.5	0.9715	0.9223
ND ^a	11/1612	0.85 (0.80–0.89)	63.0	0.97 (0.96–0.98)	71.6	155.99 (89.56–271.70)	9.2	0.9673	0.9155
RP ^a	5/186	0.96 (0.88–1.00)	0.0	0.92 (0.86–0.96)	75.1	87.80 (24.47–315.01)	0.0	0.9675	0.9158
P ^a	7/1076	0.82 (0.75–0.87)	64.2	0.95 (0.94–0.97)	79.0	154.88 (83.07–288.74)	0.0	0.9768	0.9313
R ^a	6/722	0.92 (0.87–0.95)	61.7	0.98 (0.96–0.99)	74.6	237.78 (58.60–964.82)	58.8	0.9759	0.9297
PET ^a	4/737	0.83 (0.76–0.89)	80.8	0.95 (0.92–0.96)	87.7	171.75 (79.02–373.29)	0.0	0.9775	0.9325
PET/CT ^a	9/1061	0.89 (0.84–0.93)	58.7	0.97 (0.96–0.98)	59.7	168.40 (72.64–390.42)	35.6	0.9681	0.9167

AUC, area under the curve; CI, confidence interval; DOR, diagnostic odds ratio; I², I-square (inconsistency); ND, newly diagnosed; No./no., number of included studies/number of included patients; NPC, nasopharyngeal carcinoma; P, prospective; R, retrospective; RP, recurrent primary NPC; SEN, sensitivity; SPE, specificity.

^aSubgroup analysis: there were three studies including patients with both ND and RP.

meta-analysis, the DOR values of PET or PET/CT were 193.60 for detecting lymph node metastasis and 161.12 for evaluating distant metastasis, respectively, which indicated that PET or PET/CT has a relatively high level of accuracy for N and M staging. The Q* index is the point closest to the ideal top-left corner of the SROC curve, where sensitivity and specificity are equal. These two estimates including AUC and Q* accurately reflect the diagnostic performance. Our meta-analysis showed that PET/CT performed well in both N staging (0.9734 in AUC, 0.9255 in Q* index) and M staging (0.9715 in AUC, 0.9223 in Q* index).

We should acknowledge some limitations and caveats in this meta-analysis. First of all, the exclusion of abstracts, reviews and letters may lead to publication bias. Owing to limited number of

included studies, the funnel plot analysis for assessing publication bias was not performed. Secondly, there is no well-accepted gold standard, which is a common barrier to most diagnostic studies assessing and comparing diagnostic performance of different modalities. Moreover, there was no standard follow-up strategy or time, which may affect the final diagnosis of lesions. Thirdly, patient population of included studies consisted newly diagnosed group and recurrent primary NPC group; we only performed subgroup analysis, without further analysis for the reason that the number and data of included studies was too limited. In addition, owing to the small sample and limited data of included studies, the results of subgroup analysis should be interpreted with caution. Fourth, study design of approximately 64% (14/22) of included articles were retrospective, which

Figure 1. The summary receiver operating characteristic (SROC) curves for positron emission tomography/CT in N and M staging of nasopharyngeal carcinoma on a per-patient basis. Each solid circle represents each study in the meta-analysis. The size of the circle indicates the study size. (a) SROC curve for overall assessment of staging. (b) SROC curve for N staging. (c) SROC curve for M staging. AUC, area under the curve; Q*, Q* index is the point closest to the ideal top-left corner of the SROC curve; SE, standard error.

indicated that a potential risk that imaging observers might have known the results of other modalities before assessing the PET or PET/CT results might exist.

CONCLUSIONS

Current evidence suggests that ^{18}F -FDG PET or PET/CT has good diagnostic performance for the staging or restaging of NPC, especially for N and M staging. Large, multicentre and

prospective studies with strict standardization of PET or PET/CT protocols are now needed to comprehensively assess the diagnostic value of PET or PET/CT compared with other modalities, especially MRI, for the staging of NPC.

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REFERENCES

- Palazzi M, Orlandi E, Bossi P, Pignoli E, Potepan P, Guzzo M, et al. Further improvement in outcomes of nasopharyngeal carcinoma with optimized radiotherapy and induction plus concomitant chemotherapy: an update of the Milan experience. *Int J Radiat Oncol Biol Phys* 2009; **74**: 774–80. doi: [10.1016/j.ijrobp.2008.08.068](https://doi.org/10.1016/j.ijrobp.2008.08.068)
- Chong VF, Fan YF. Detection of recurrent nasopharyngeal carcinoma: MR imaging versus CT. *Radiology* 1997; **202**: 463–70.
- Chin SC, Fatterpekar G, Chen CY, Som PM. MR imaging of diverse manifestations of nasopharyngeal carcinomas. *AJR Am J Roentgenol* 2003; **180**: 1715–22.
- Chan AT. Nasopharyngeal carcinoma. *Ann Oncol* 2010; **21**: vii308–12. doi: [10.1093/annonc/mdq277](https://doi.org/10.1093/annonc/mdq277)
- Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized intergroup study 0099. *J Clin Oncol* 1998; **16**: 1310–17.
- Smythe WR. Treatment of stage I and II non-small-cell lung cancer. *Cancer Control* 2001; **8**: 318–25.
- Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. *N Engl J Med* 2001; **345**: 1890–900.
- Kao CH, ChangLai SP, Chieng PU, Yen RF, Yen TC. Detection of recurrent or persistent nasopharyngeal carcinomas after radiotherapy with 18-fluoro-2-deoxyglucose positron emission tomography and comparison with computed tomography. *J Clin Oncol* 1998; **16**: 3550–5.
- Anzai Y, Carroll WR, Quint DJ, Bradford CR, Minoshima S, Wolf GT, et al. Recurrence of head and neck cancer after surgery or irradiation: prospective comparison of 2-deoxy-2-[F-18] fluoro-d-glucose PET and MR imaging diagnoses. *Radiology* 1996; **200**: 135–41.
- Ng SH, Chan SC, Yen TC, Chang J, Liao CT, Ko SF, et al. Staging of untreated nasopharyngeal carcinoma with PET/CT: comparison with conventional imaging work-up. *Eur J Nucl Med Mol Imaging* 2009; **36**: 12–22. doi: [10.1007/s00259-008-0918-7](https://doi.org/10.1007/s00259-008-0918-7)
- Hu WH, Zhang GY, Liu LZ, Wu HB, Li L, Gao YH, et al. Comparison between PET-CT and MRI in diagnosing nodal metastasis of nasopharyngeal carcinoma. [In Chinese.] *Chin J Cancer* 2005; **24**: 855–60.
- Zhang GY, Hu WH, Liu LZ, Wu HB, Gao YH, Li L, et al. Comparison between PET/CT and MRI in diagnosing lymph node metastasis and N staging of nasopharyngeal carcinoma. [In Chinese.] *Chinese J Oncol* 2006; **28**: 381–4.
- Wang CP, Lee CY, Lou PJ, Yen RF, Hsiao JK, Ko JY. Role of ultrasound-guided fine needle aspiration in assessing the impalpable cervical node with increased 18F-fluorodeoxyglucose uptake on positron emission tomography scanning: preliminary communication. *J Laryngol Otol* 2008; **122**: 1349–53. doi: [10.1017/S0022215108002727](https://doi.org/10.1017/S0022215108002727)
- Ng SH, Chan SC, Yen TC, Chang JT, Liao CT, Ko SF, et al. Pretreatment evaluation of distant-site status in patients with nasopharyngeal carcinoma: accuracy of whole-body MRI at 3-Tesla and FDG-PET-CT. *Eur Radiol* 2009; **19**: 2965–76. doi: [10.1007/s00330-009-1504-5](https://doi.org/10.1007/s00330-009-1504-5)
- Chua ML, Ong SC, Wee JT, Ng DC, Gao F, Tan TW, et al. Comparison of 4 modalities for distant metastasis staging in endemic nasopharyngeal carcinoma. *Head Neck* 2009; **31**: 346–54. doi: [10.1002/hed.20974](https://doi.org/10.1002/hed.20974)
- Whiting PF, Weswood ME, Rutjes AW, Reitsma JB, Bossuyt PN, Kleijnen J. Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. *BMC Med Res Methodol* 2006; **6**: 9.
- Zamora J, Abaira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol* 2006; **6**: 31.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539–58.
- Zhang GY, Wei WH, Li YZ, Xu T, Wu HB, Wang QS, et al. The role of PET-CT in diagnosing distant metastasis of nasopharyngeal carcinoma. [In Chinese.] *Cancer Res Clin* 2011; **23**: 294–8.
- Xu QL, Chen F, Wan WX. The diagnostic value of 18F-FDG PET/CT for recurrence or distant metastasis in nasopharyngeal carcinoma patients. [In Chinese.] *Guide Chin Med* 2011; **09**: 341–4.
- Sun XR, Fan W. *The retropharyngeal lymph node metastasis diagnostic criteria and the spread pattern in nasopharyngeal carcinoma based on 18F-FDG PET/CT*. MD thesis. Guangdong: Sun Yat-Sen University; 2010.
- Shen C, Liu CY, Yao SZ. Application of 18F-FDG PET/CT in the follow-up of nasopharyngeal carcinoma after treatment. [In Chinese.] *J Med Imaging* 2007; **17**: 674–6.
- Lin Q, Li YM, Zhou Y, Xu CD, Sun L, Zhao L, et al. The value of 18F-FDG PET/CT in N staging nasopharyngeal carcinoma patients. [In Chinese.] *Chin J Nucl Mol Imaging* 2012; **32**: 418–21.
- Hu XQ, Xiao WW, Shen GZ, Han F, Lu LX, Xu AA, et al. Clinical value of pretreatment 18F-FDG PET/CT for small cervical lymph node in nasopharyngeal carcinoma patients. [In Chinese.] *Chin J Clin (Electron Ed)* 2012; **6**: 1425–9.
- Yen TC, Chang JT, Ng SH, Chang YC, Chan SC, Lin KJ, et al. The value of 18F-FDG PET in the detection of stage M0 carcinoma of the nasopharynx. *J Nucl Med* 2005; **46**: 405–10.
- Liu FY, Lin CY, Chang JT, Ng SH, Chin SC, Wang HM, et al. F-18-FDG PET can replace conventional work-up in primary M staging of nonkeratinizing nasopharyngeal carcinoma. *J Nucl Med* 2007; **48**: 1614–19.
- Liu FY, Chang JT, Wang HM, Liao CT, Kang CJ, Ng SH, et al. [18F]fluorodeoxyglucose positron emission tomography is more sensitive than skeletal scintigraphy for detecting bone metastasis in endemic nasopharyngeal carcinoma at initial staging. *J Clin Oncol* 2006; **24**: 599–604.
- Lin SX, Li X, Wu H, Lu J, Liang B, Peng X, et al. Efficiency comparison between PET/CT and conventional work-up for evaluating

- distant metastasis of nasopharyngeal carcinoma. [In Chinese.] *J Clin Otorhinolaryngol Head Neck Surg* 2012; **26**: 529–32.
29. Li TR, Du XK, Huo TL, Zhao CL. 18F-FDG PET/CT imaging in patients with nasopharyngeal carcinoma: distant metastasis and recurrence. *J Chin Clin Med* 2010; **5**: 703–11.
 30. Comoretto M, Balestreri L, Borsatti E, Cimitan M, Franchin G, Lise M. Detection and restaging of residual and/or recurrent nasopharyngeal carcinoma after chemotherapy and radiation therapy: comparison of MR imaging and FDG PET/CT. *Radiology* 2010; **249**: 203–11. doi: [10.1148/radiol.2491071753](https://doi.org/10.1148/radiol.2491071753)
 31. Chen YK, Su CT, Ding HJ, Chi KH, Liang JA, Shen YY, et al. Clinical usefulness of fused PET/CT compared with PET alone or CT alone in nasopharyngeal carcinoma patients. *Anticancer Res* 2006; **26**: 1471–7.
 32. Chang JT, Chan SC, Yen TC, Liao CT, Lin CY, Lin KJ, et al. Nasopharyngeal carcinoma staging by (18)F-fluorodeoxyglucose positron emission tomography. *Int J Radiat Oncol Biol Phys* 2005; **62**: 501–7.
 33. Yen RF, Hong RL, Tzen KY, Pan MH, Chen TH. Whole-body 18F-FDG PET in recurrent or metastatic nasopharyngeal carcinoma. *J Nucl Med* 2005; **46**: 770–4.
 34. Lim TC, Chua ML, Chia GS, Ng DC, Ong SC, Wee JT, et al. Comparison of MRI, CT and 18F-FDG-PET/CT for the detection of intracranial disease extension in nasopharyngeal carcinoma. *Head Neck Oncol* 2012; **4**: 49.
 35. Ng SH, Joseph CT, Chan SC, Sheung-Fat K, Hung-Ming W, Chun-Ta L, et al. Clinical usefulness of 18F-FDG PET in nasopharyngeal carcinoma patients with questionable MRI findings for recurrence. *J Nucl Med* 2004; **45**: 1669–76.
 36. Nishioka T, Shiga T, Shirato H, Tsukamoto E, Tsuchiya K, Kato T, et al. Image fusion between 18FDG-PET and MRI/CT for radiotherapy planning of oropharyngeal and nasopharyngeal carcinomas. *Int J Radiat Oncol Biol Phys* 2002; **53**: 1051–7.
 37. Lee AW, Law SC, Foo W, Pooh YF, Cheung FK, Chan DK, et al. Retrospective analysis of patients with nasopharyngeal carcinoma treated during 1976–1985: survival after local recurrence. *Int J Radiat Oncol Biol Phys* 1993; **26**: 773–82.
 38. Yoo J, Henderson S, Walker-Dilks C. Evidence-based guideline recommendations on the use of positron emission tomography imaging in head and neck cancer. *Clin Oncol (R Coll Radiol)* 2013; **25**: e33–66.
 39. Boellaard R, O'Doherty MJ, Weber WA, Mottaghy FM, Lonsdale MN, Stroobants SG, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. *Eur J Nucl Med Mol Imaging* 2010; **37**: 181–200. doi: [10.1007/s00259-009-1297-4](https://doi.org/10.1007/s00259-009-1297-4)
 40. Delbeke D, Coleman RE, Guiberteau MJ, Brown ML, Royal HD, Siegel BA, et al. Procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0. *J Nucl Med* 2006; **47**: 885–95.
 41. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol* 2003; **56**: 1129–35.