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Original Article

Comparison of MRI, CT and 18F-FDG PET/CT in the diagnosis of local and metastatic of nasopharyngeal carcinomas: an updated meta analysis of clinical studies

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Abstract: Background: A meta-analysis was conducted to evaluate the accuracy of MRI, CT and FDG PET/CT in TNM stage of nasopharyngeal carcinoma patients (NPC). Methods: Through a search of studies from 1996 to April 2015, pooled estimated sensitivity, specificity, pooled diagnostic odds ratio (DOR), summary receiver operating characteristic (SROC) curves and Q*-index were calculated. Results: Totally 23 studies were included for analysis. In T stage, the pooled sensitivity, specificity, DOR and SROC of MRI were 0.95 (95% CI 0.93-0.97), 0.76 (95% CI 0.71-0.80), 86.85 (16.36-461.06) and 0.9213 (SE 0.0372) respectively. The pooled sensitivity, specificity, DOR and SROC of CT were 0.84 (95% CI 0.79 to 0.88), 0.80 (95% CI 0.71 to 0.88), 6.32 (1.17 to 34.02) and 0.7215 (SE 0.054) respectively. The pooled sensitivity, specificity, DOR and SROC of FDG PET/CT were 0.85 (95% CI 0.76 to 0.91), 0.91 (95% CI 0.84 to 0.96) and 0.8673 (SE 0.0311). In N stage, the pooled sensitivity, specificity, DOR and SROC of MRI were 0.88 (95% CI 0.85-0.90), 0.95 (95% CI 0.93-0.97), 93.68 (23.21-379.69) and 0.9153 (SE 0.099) respectively. The pooled sensitivity, specificity, DOR and SROC of CT were 0.92 (95% CI 0.88-0.95), 0.93 (0.76-0.99), 93.81 (22.39-393.03) and 0.8872 (SE 0.0520) respectively. The pooled sensitivity, specificity, DOR and SROC of FDG PET/CT were 0.88 (95% CI 0.85-0.90), 0.95 (95% CI 0.93-0.97), 93.88 (23.21-379.69) and 0.9153 (SE 0.0299) respectively. In M stage, the pooled sensitivity and specificity of MRI were 0.53 (95% CI 0.35-0.70) and 0.99 (95% 0.95-1.00). The pooled sensitivity and specificity of CT were 0.80 (95% CI 0.44-0.97) and 0.93 (95% CI 0.86-0.97) respectively. The pooled sensitivity, specificity and SROC of FDG PET/CT were 0.82 (95% 0.74-0.88), 0.98 (95% CI 0.96-0.99) and 0.9002 (SE 0.075) respectively. Conclusion: The analysis suggested that MRI had good accuracy in diagnosis of T stage. Whereas CT is currently a good performance in diagnosis of N stage, FDG PET/CT shows good accuracy in diagnosis of M stage.

Keywords: Meta-analysis, MRI, CT, FDG PET/CT, nasopharyngeal carcinoma

Introduction

Nasopharyngeal carcinoma (NPC) is globally an uncommon cancer with approximately 80.000 new cases reported per year and accounting 0.7% of all cancer. Even though the incidence rate is less than 1 case per 100,000 population in North American and Europe, In endemic areas like Southern China (e.g. Hong Kong) and Southeast Asia, the annual age-standardized incidence rates are as high as 20 to 30 cases per 100,000 population in men and 8 to 15 cases per 100,000 populations in women [1]. NPC is an aggressive head and neck cancer with a high incidence of loco-regional spread and of distant metastasis at presentation. NPC may spread locally to involve the parapharyngeal soft tissue base of skull or intracranial structures. The nasopharynx has a rich lymphatic plexus; 75% of patients present with enlarged cervical nodes, 80% of whom have bilateral involvement. NPC has a relative high incidence of systemic metastasis (up to 41%) when compared with the other head and neck

tumor (5-24%). The most common sites of metastasis are bone (20%), lung (13%), and liver (9%) [2].

Owing to the specific anatomic location and highly responsive to radiation, the main treatment of NPC is radiotherapy and chemotherapy. Staging of patients affected with NPC represents the basic step to successful treatment. The accurate diagnosis of the tumor extension and the delineation of target volume mostly depend on imaging.

The American Joint Committee on Cancer (AJCC) T (primary tumor) N (Regional lymph nodes) M (Distant Metastasis) system is one of the most widely used staging system internationally [3]. The National Comprehensive Cancer Network (NCCN) guidelines recommend MRI of the nasopharynx and neck as well as CT scan for T and N classification. For patients with N and M classifications, it suggests that FDG PET/CT scan may be considered [4]. The aim of this study was to analyze the sensitivity, specificity and accuracy of MRI, CT and FDG PET/CT in staging NPC patients.

Materials and methods

Search strategy and study selection

We searched MEDLINE, EMBASE and Chinese national knowledge infrastructure (CNKI) from 1996 to April 2015. The search strategy was based on the combination of the following keywords: 1) MRI or magnetic resonance; 2) CT or computed tomography; 3) FDG PET/CT or FDG positron emission tomography; 4) nasopharyngeal carcinoma or metastasis of nasopharynx or lymph node; 5) detection or staging or accuracy. Conference abstracts and letters to the journal editors were excluded because they contained limited data. Two reviewers independently judged study eligibility and disagreements were resolved by discussion and if necessary by a third reviewer.

The included criteria were: 1) histopathology analysis or clinical and imaging follow-up or compared with reference standard were used as reference standard; 2) only studies which a 2X2 table could be constructed for true-positive, true-negative, false-positive and false-negative values were included; 4) the studies were based on per patient statistics; 5) when data or subsets of data were presented in more than one articles, the article with the most detail or the most recent article was chosen; 6) the studies including at least 10 patients were selected for inclusion in the study since very small studies may be vulnerable to selection bias.

Data extraction

Two reviewers extracted data from each eligible study independently using standardized data extraction form and any disagreement were resolved by discussion or by appeal to a third reviewer.

Reviewer were not blinded with regard to information about the journal name, the authors, country of origin or the year of publication; as this has been shown to the unnecessary [5]. In addition, more information (sample size, age, gender distribution, stage of patients and reference test used to define the stage of the disease. Publications investigating more than one aspect of classification were analyzed independently. The number of cases was only extracted with true positive, true negative, false negative and false positive.

We assess the methodological quality of the studies using the quality assessment for studies of diagnostic accuracy (QUADAS) tool [6]. Fourteen items in QUADAS tool examined potential sources of bias in diagnostic studies in a systematic evidence-based manner. Higher scores suggest lower risk of bias in the study's methodology.

Statistical analysis

The accuracy of 4 modality in 3 staging of NPC patients was determined by combined estimate of sensitivity and specificity, pooled diagnostic odds ratio (DOR), summary receiver operating characteristic (SROC) curves and Q*-index. The degree of heterogeneity in included studies was analyzed by Cochran chi-square statistic. A random effect model was applied while significant heterogeneity was observed ($p<0.05$). A random effects meta-regression model was used to compare subgroup estimates. SROC graph gives us a globe estimate of diagnostic test's performance and illustrates the tradeoff between sensitivity and specificity [7]. Q*-index reflects the diagnostic value and is the best statistical summary method. Moreover, the diagnostic odds ratio (DOR) indicates the test accuracy that transfers the sensitivity and specificity into a number. The higher DOR

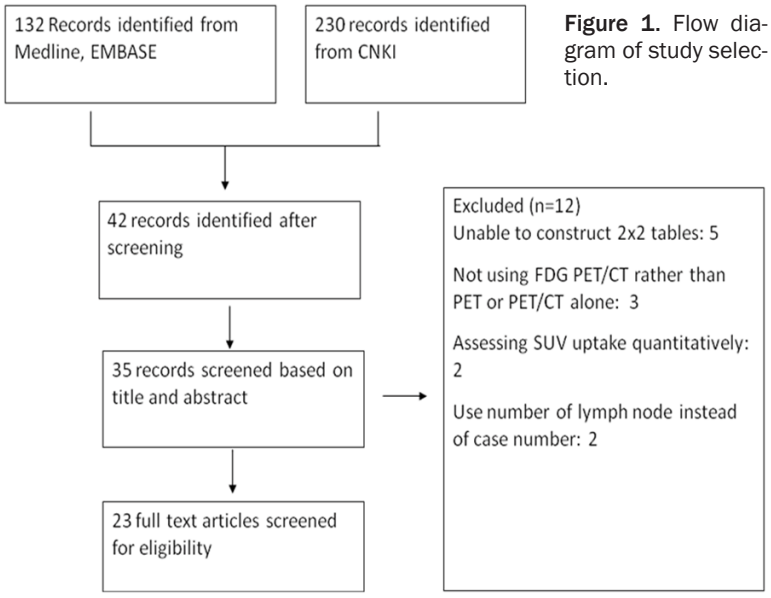

Figure 1. Flow diagram of study selection.

value indicates better accuracy which is better discriminatory test performance. A value of 1.0 indicates that the test does not discriminate between patients between with and without malignance in each classification.

All these analysis were performed using METADISC version 1.4 (XI Conchrane Colloquium, Barcelona, Spain) and level of significance set at 5%. The paired and inter-related comparison showed by sensitivity and specificity estimated the accuracy, both are reported simultaneously. Diagnositc odd ratio (DOR) is very useful in procedures like meta-regression. If heterogeneity is found to present from analysis, Meta-regression is used to explore the reason for such heterogeneity by relating study level covariates to an accuracy measure. DOR is used to globally compare the overall diagnostic accuracy of different tests. The overall DOR is estimated by combining individual DORs through Mantel-haenszel or the DerSimonian Laird methods and then fits an SROC curve. The estimation of AUC and the Q* index, along with their standard errors can summarize measure of global accuracy and aids inter-test comparisons.

Results

Study selection and description

We identified 23 studies including 2413 patients using search strategy summarized in **Figure 1**. Ten studies addressed the T stage (local extent of the primary tumor) including 8 studies with MRI, 4 studies with CT and 6 studies with FDG PET/CT. Twelve studies were included in the analysis of N stage (lymph node metastasis). Among 12 studies, 10 studies of MRI test cases, 4 studies of CT test and 12 studies of FDG PET/CT test cases. Seven studies were analyzed in M stage (distant metastasis), which has 2 studies about whole body MRI, 2 studies about CT and 8 studies about FDG PET/CT.

Eleven studies were published in the English language [8-18] while twelve studies in Chinese language [18-30]. The characteristics of the 23 studies are summarized in **Table 1**. In T classification, 884 patients were included in MRI test, 335 patients in CT test and 257 patients in FDG PET/CT test. In N classification, 1216 patients were included in MRI, while 290 patients in CT test and 1229 patients in FDG PET/CT. In M classification, 261 patients were included in MRI test and 98 patients in CT test while 1009 patients in FDG PET/CT test. The mean age of the included patients was 48.2 years and approximately 69.9% were male. Nine studies included patients of T stage [9, 11-13, 15, 18, 21, 25, 30], twelve studies included patients of N stage [9, 11, 19, 22, 24, 26-30], and eight studies included patients of M stage [8-10, 14, 16, 17, 19, 20].

Quality assessment showed moderate quality scores of the included studies with a medium score (**Table 1**). Studies exploring more than one aspect of classification were assessed independently for quality. The methodological quality was high in Tang study (QUADAS score ≥13 [14], moderate in fourteen studies (QUADAS 10-12) [8, 9, 12, 13, 15, 16, 18, 21, 24-27, 29] and low in eight studies (QUADAS<10) [10, 11, 17, 19, 20, 22, 23, 30]. Most studies did not describe question 11 and question 12 clearly.

Accuracy

T classification: In MRI, the combined data from eight available studies revealed a sensitivity of

Table 1. Characteristics of included studies

Study	Patient number	Median age	Male (%)	Language	Classification	QUADAS	Reference standard
Chen 2006 [9]	20	46.3	70	En	T, N, M	10	Nasoscope and CT/MR and clinical follow-up
Chua 2009 [10]	78	50	76.9	En	M	9	Histological proof, Clinical follow-up for 6 month
Comoretto 2008 [11]	63	52	69.8	En	T, N	8	Pathologic evaluation and follow up for at least 6 month
Gao 2014 [12]	150	48	66	En	T	10	Sonography or endoscopic biopsy
King 2011 [13]	246	50	59.8	En	T	12	Endoscope biopsy
Tang 2013 [14]	583	46	81.3	En	M	13	Conventional work-up (CWU)
Lim 2012 [15]	78	51	76.9	En	T	10	Histological proof
Ng 2009 [16]	111	48.9	75.7	En	M	10	Histological analysis or close clinical and imaging follow-up for 12 month
Ng 2009 [8]	150	48.17	74	En	M	11	Histological analysis or close clinical and imaging follow-up for 12 month
Iagaru 2011 [17]	26	47.3	69.2	En	M	9	Clinical follow-up
Ma 2009 [18]	57	46	82.4	En	T	12	Clinical symptom or MRI or CT
Shen 2007 [20]	23	50	69.7	Ch	M	9	Endoscope biopsy and follow-up
Zhang 2010 [21]	13	46.7	61.9	Ch	T, N	11	Histology, biopsy and follow-up
Wang 2007 [22]	18	52	60.5	Ch	N	8	CT and MRI
Wang 2014 [23]	60	52	60.5	Ch	N	9	Histology biopsy
Huang 2013 [24]	80	49.2	70	Ch	N	11	Histology proof and follow up
Cai 2011 [25]	25	50	64	CH	T	12	Clinical findings, MRI or CT
Hu 2005 [26]	105	43	78.1	Ch	N	10	Histology and follow-up
Zhang 2006 [27]	116	51	79.3	Ch	N	10	Follow up
Lin 2008 [28]	68	41	58.8	Ch	N	11	MRI neck
Su 2006 [29]	53	40	68	Ch	N	11	MRI-looking at retropharyngeal LN
Sun 2005 [30]	249	45	75	Ch	T, N	9	Follow-up
Lin 2009 [19]	41	52.3	60.9	Ch	N, M	6	Clinical follow-up

0.95 (95% CI 0.93-0.97) and specificity of 0.76 (95% CI 0.71-0.80). The pooled diagnostic odds ratio (DOR) was 86.85 (16.36-461.06). The Q*-index was 0.9213 (SE 0.0372) (**Figure 2**). As regard as CT, the four included studies were combined and evaluation of T classification showed sensitivity of 0.84 (95% CI 0.79 to 0.88) and specificity of 0.80 (95% CI 0.71 to 0.88). While the pooled DOR is 6.32 (1.17 to 34.02) and Q*-index was 0.7215 (SE 0.054) (**Figure 3**). In terms of FDG PET/CT, The combined four studies indicate a sensitivity of 0.85 (95% CI 0.76 to 0.91), and specificity of 0.91 (95% CI 0.84 to 0.96). The Q*-index was 0.8673 (SE 0.0311) (**Figure 4**). Compared to MRI, the sensitivity of CT and FDG PET/CT was lower (0.95 *vs* 0.84 and 0.85).

N classification: The combined sensitivity of MRI estimated for N classification in ten studies is 0.88 (95% CI 0.85-0.90) and specificity is 0.95 (95% CI 0.93-0.97). The pooled DOR of MRI was 93.68 (23.21-379.69) and Q*-index was 0.9153 (SE 0.099) (**Figure 5**). Whereas the combined four studies in CT detection revealed the sensitivity and specificity are 0.92 (95% CI 0.88-0.95) and 0.93 (0.76-0.99) separately. The pooled DOR of CT was 93.81 (22.39-393.03) and Q*-index was 0.8872 (SE 0.0520) (**Figure 6**). The combined ten studies of FDG PET/CT showed that sensitivity is 0.88 (95% CI 0.85-0.90) and specificity is 0.95 (95% CI 0.93-0.97). The pooled DOR was 93.88 (23.21-379.69) and Q*-index was 0.9153 (SE 0.0299) (**Figure 7**). The reference standard used among the studies varied. One study used MRI neck [28]. Six studies required Histology and Pathology biopsy or nasoscope [9, 11, 21, 23, 24, 26]. Four studies relied on clinical follow-up [19, 21, 26, 27, 30].

There is no difference of sensitivity between individual studies on CT no matter what reference standard was used in the studies (p=0.0578). The effect on sensitivity was higher for studies on CT than that on MRI and FDG PET/CT (0.92 vs 0.82 and 0.88). Whereas, specificity showed significant difference among studies in FDG PET/CT and MRI, but did not show difference among studies in CT (p= 0.9500).

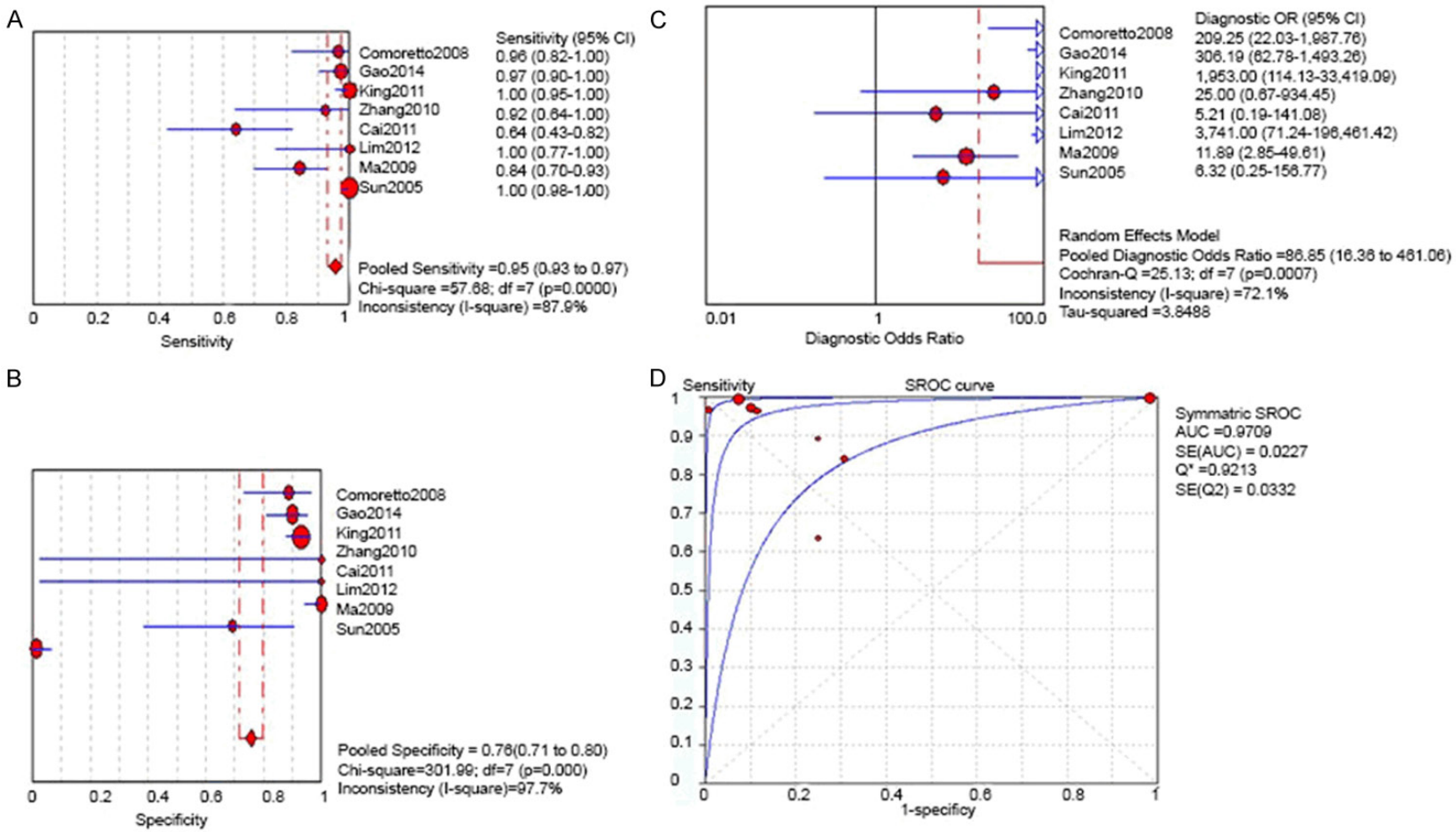

Figure 2. For T Classification by MRI: A. Pooled sensitivity; B. Pooled specitficity; C. Pooled diagnostic odds ratio; D. Summary receiver operating Characteristic (SROC) curve with Q*-index.

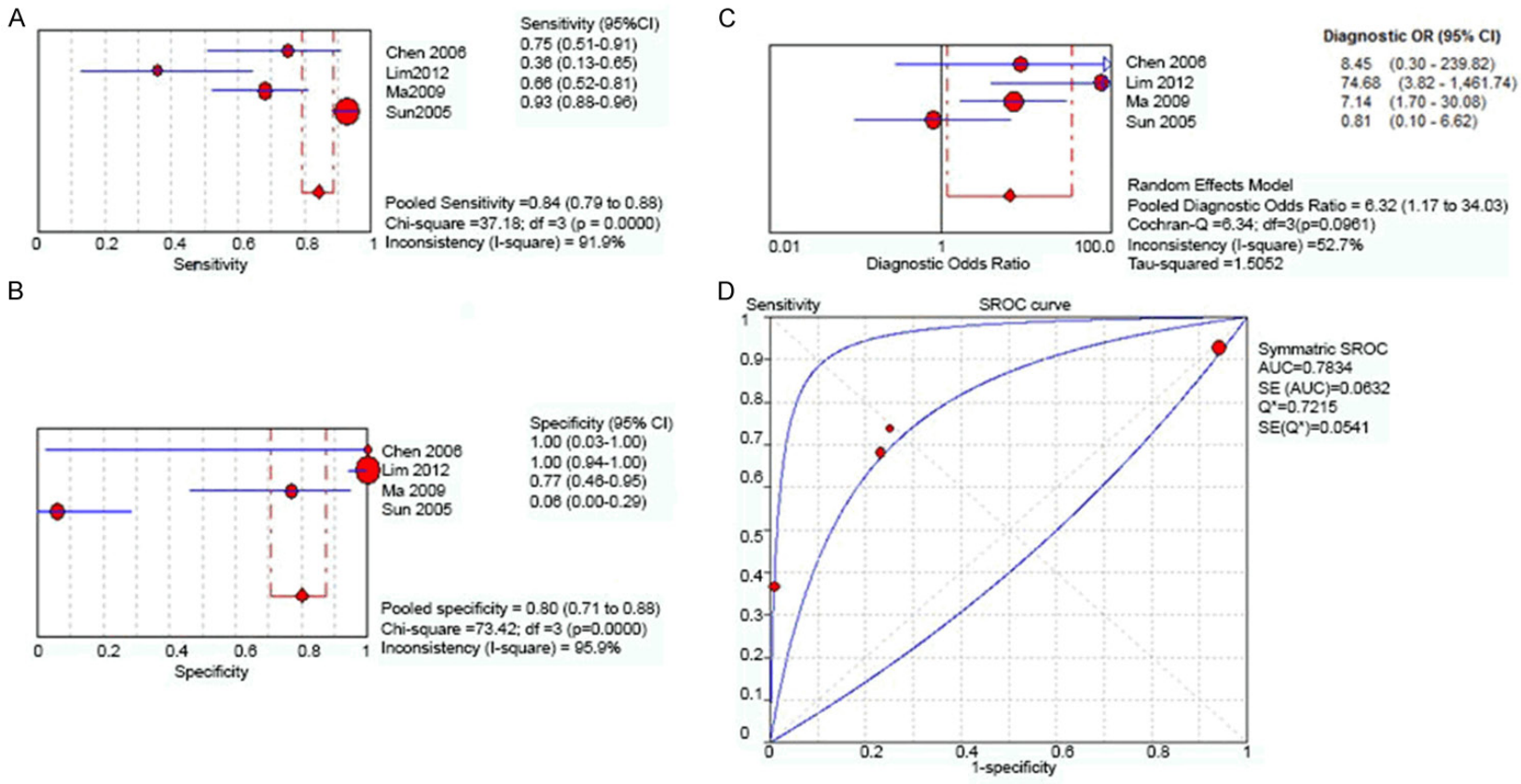

Figure 3. For T Classification by CT: A. Pooled sensitivity; B. Pooled specitficity; C. Pooled diagnostic odds ratio; D. Summary receiver operating Characteristic (SROC) curve with Q*-index.

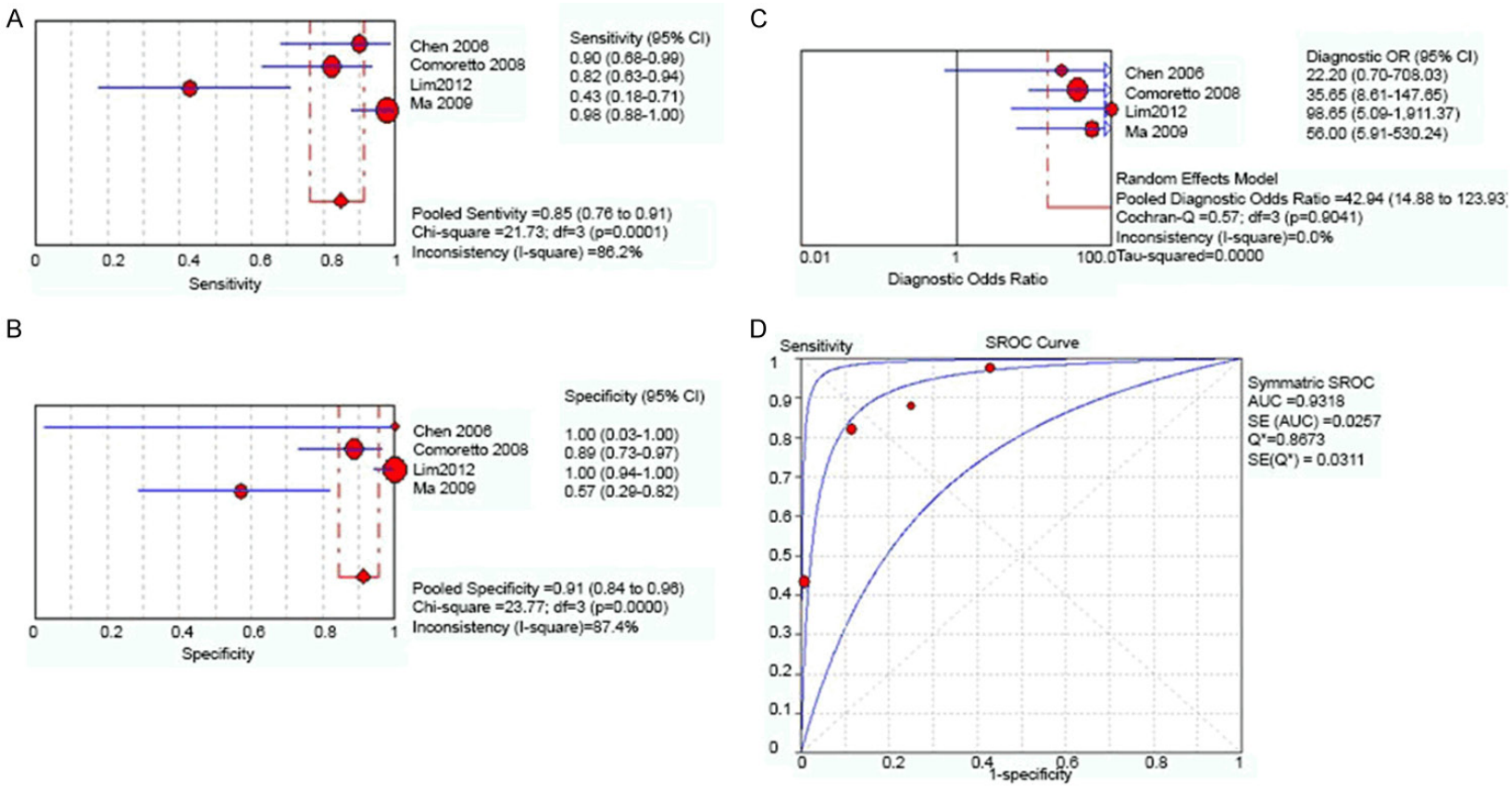

Figure 4. For T Classification by FDG PET/CT: A. Pooled sensitivity; B. Pooled specitficity; C. Pooled diagnostic odds ratio; D. Summary receiver operating Characteristic (SROC) curve with Q*-index.

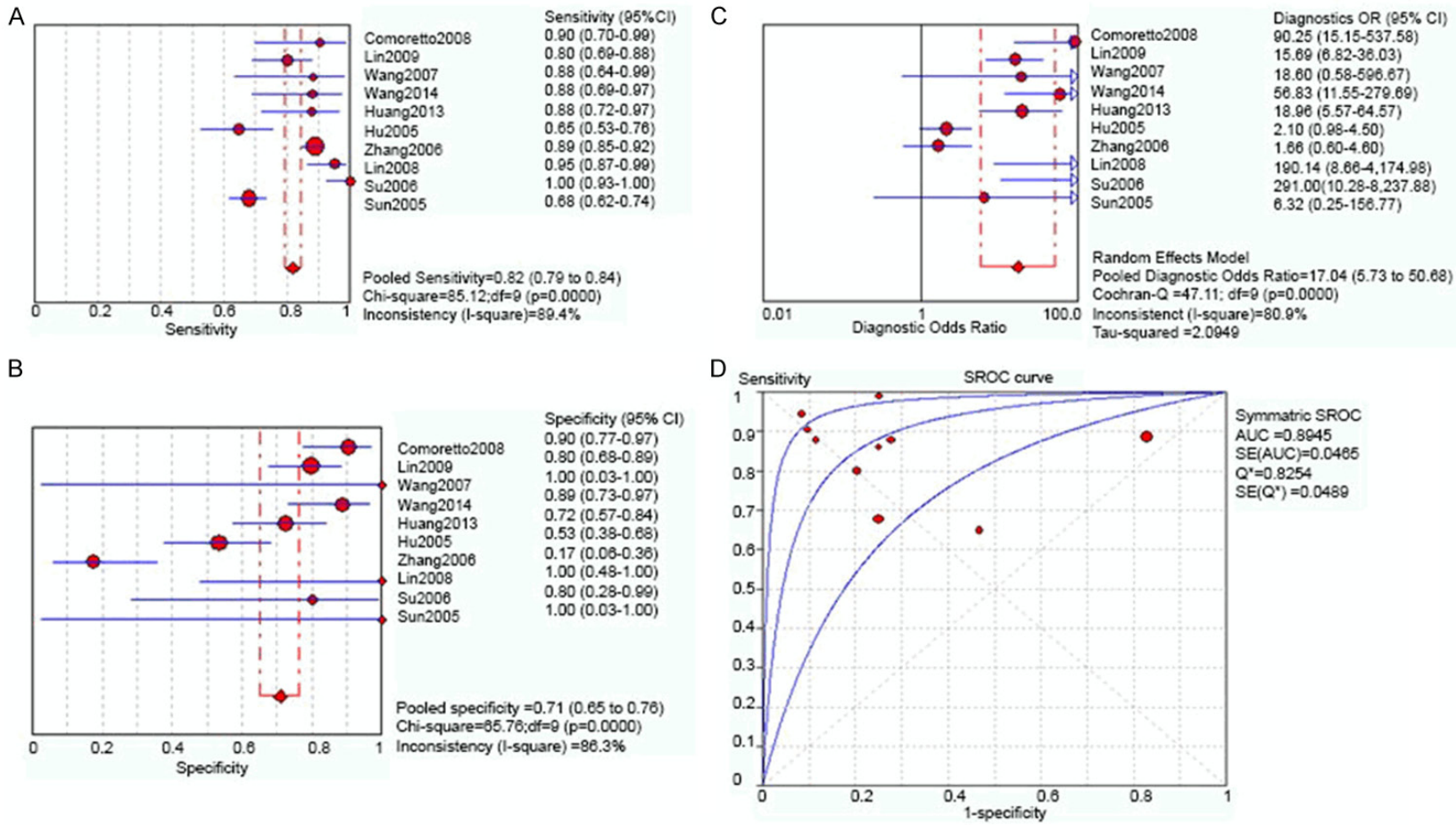

Figure 5. For N Classification by MRI: A. Pooled sensitivity; B. Pooled specitficity; C. Pooled diagnostic odds ratio; D. Summary receiver operating Characteristic (SROC) curve with Q*-index.

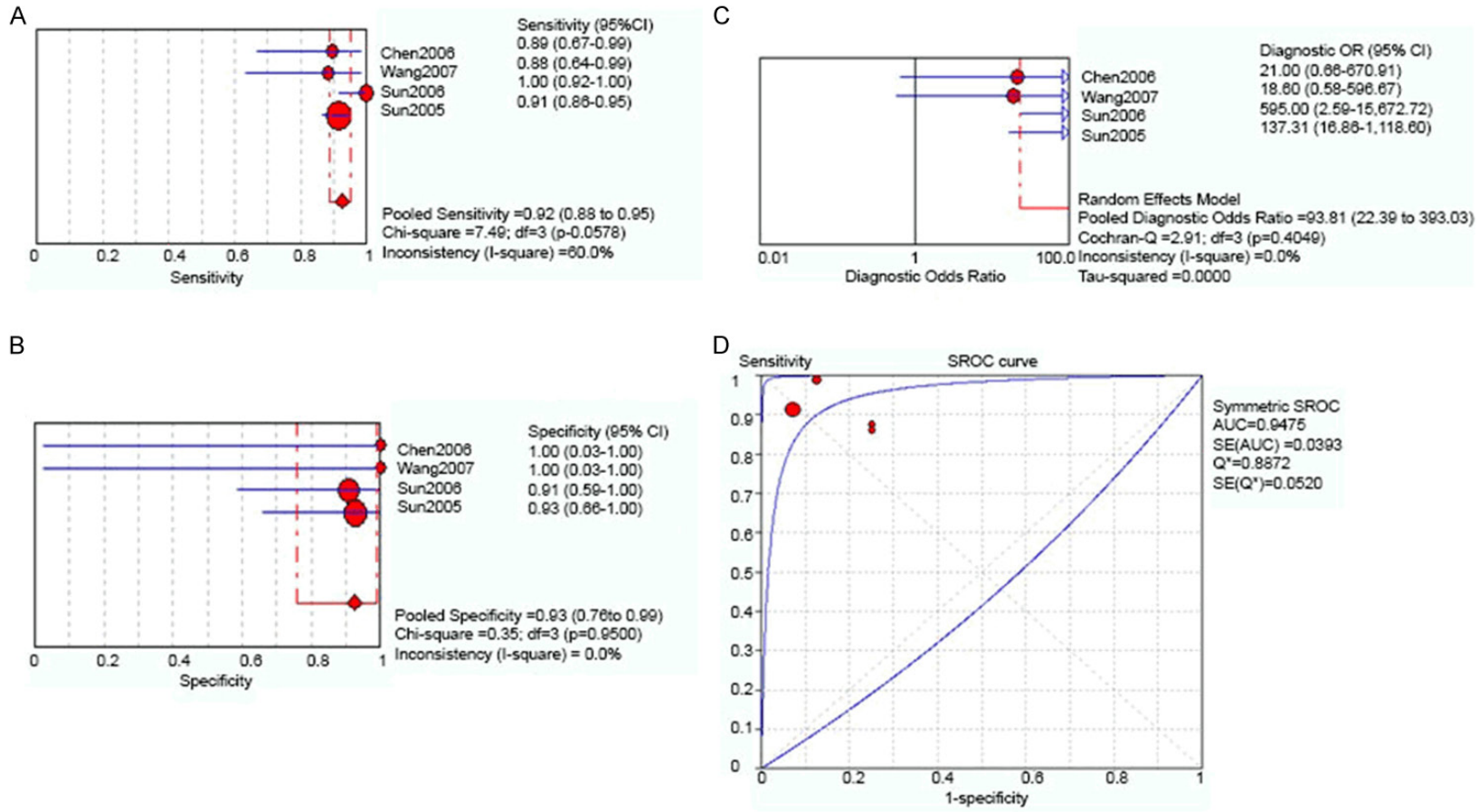

Figure 6. For N Classification by CT: A. Pooled sensitivity; B. Pooled specitficity; C. Pooled diagnostic odds ratio; D. Summary receiver operating Characteristic (SROC) curve with Q*-index.

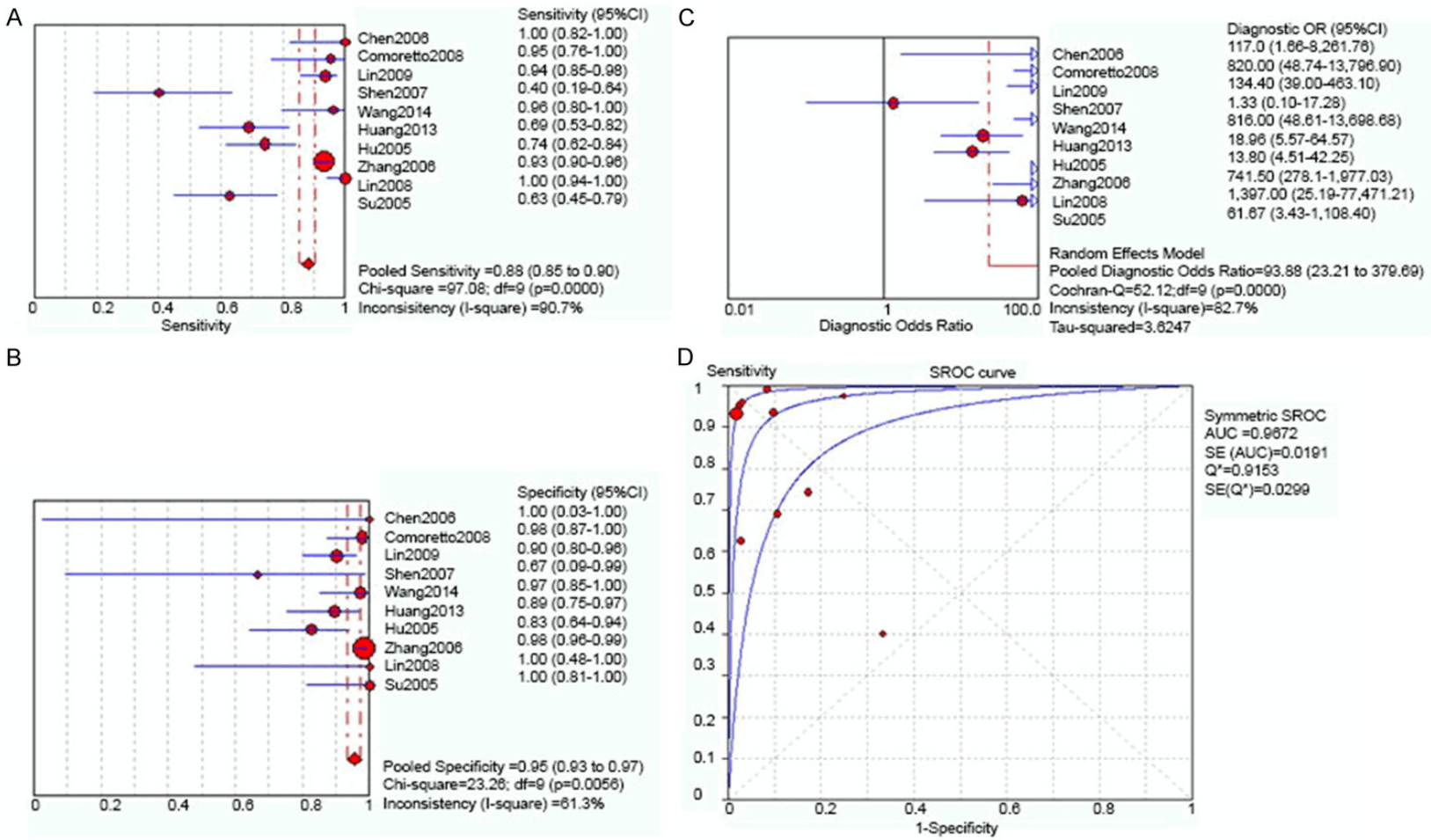

Figure 7. For N Classification by FDG PET/CT: A. Pooled sensitivity; B. Pooled specitficity; C. Pooled diagnostic odds ratio; D. Summary receiver operating Characteristic (SROC) curve with Q*-index.

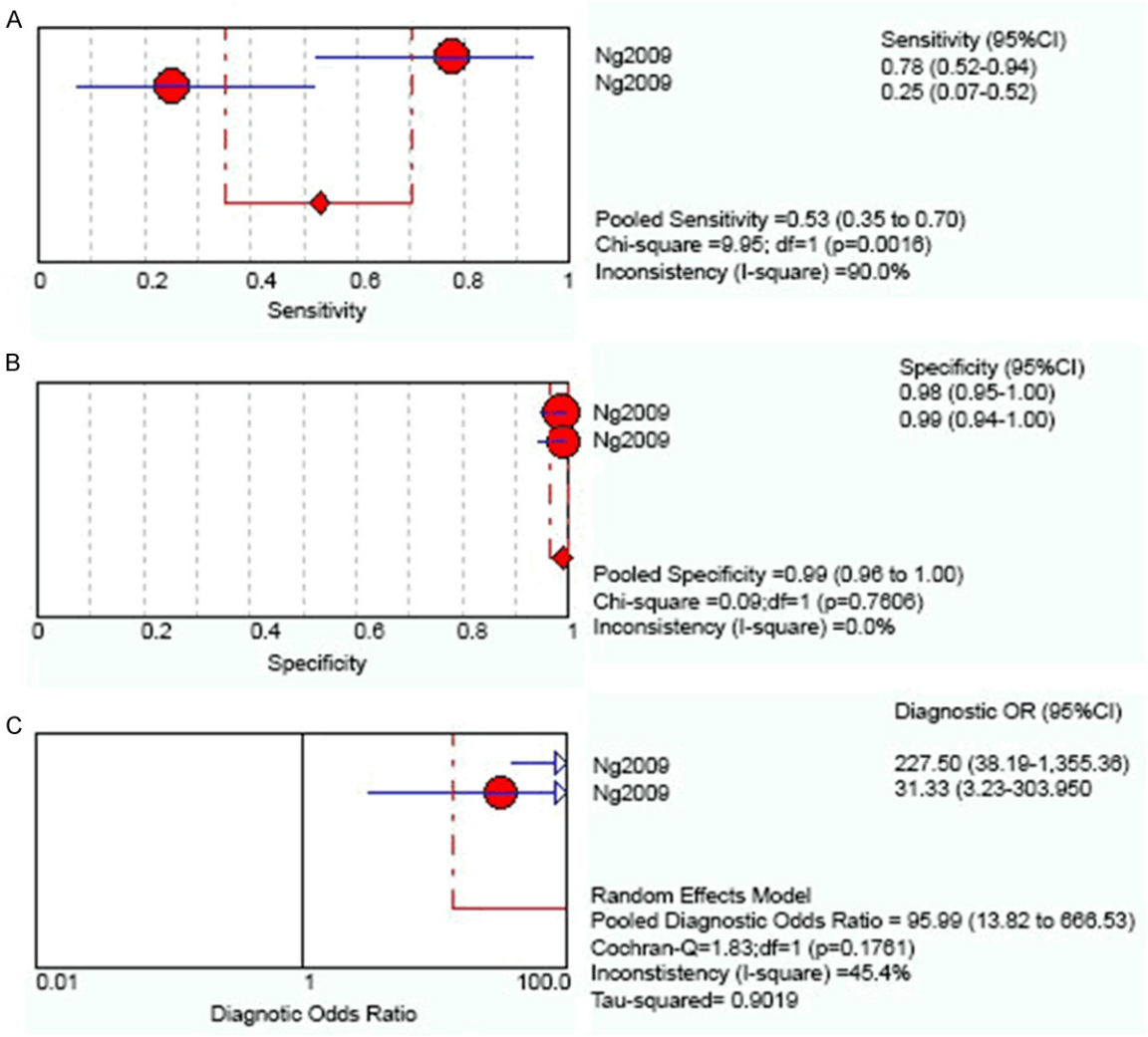

Figure 8. For M Classification by MRI: A. Pooled sensitivity; B. Pooled specitficity; C. Pooled diagnostic odds ratio.

M classification: The combined sensitivity estimate for MRI is 0.53 (95% CI 0.35-0.70) (**Firgure 8**), for CT is 0.80 (95% CI 0.44-0.97) (**Figure 9**), whereas the combined sensitivity for FDG PET/CT is 0.82 (95% 0.74-0.88) (**Figure 10**). The specificity of MRI, CT and FDG PET/CT is 0.99 (95% 0.95-1.00), 0.93 (95% CI 0.86-0.97) and 0.98 (95% CI 0.96-0.99) respectively. Since only two studies were included on MRI and CT test, no Q*-index was available. Q*-index of studies on FDG PET/CT is 0.9002 (SE 0.075) (**Figure 10**). All the studies relied on clinical follow-up. Sensitivity of FDG PET/CT is higher than that of MRI and CT (0.82 vs 0.53 and 0.80).

Discussion

TNM stage is the major prognostic factor of patient survival in NPC [31-33]. In this analysis, MRI has high sensitivity (0.95 (95% CI 0.93-0.97)) than CT and FDG PET/CT in T stage, which indicated that MRI can provide a more accurate evaluation of the extent of the primary tumor. This result is consistent with Patriza study [34]. MRI can identify as retropharyngeal nodes finding previously misdiagnosed on CT as oropharyngeal or parapharngeal invasion. Since MRI has a good capacity to depict the detailed anatomic information, MRI has been widely used in the management of NPC.

In N stage, retropharyngeal node are involved in NPC, presented in 72% NPC patients with nodal disease [15]. The metastasis of cervical lymph nodes is frequently and presented in 60-88.1% NPC patients in regional node involvement [35, 36]. This analysis showed that sensitivity of CT (0.92 (95% CI 0.88-0.95)) is higher than MRI (0.88 (95% CI 0.85-0.90)) and

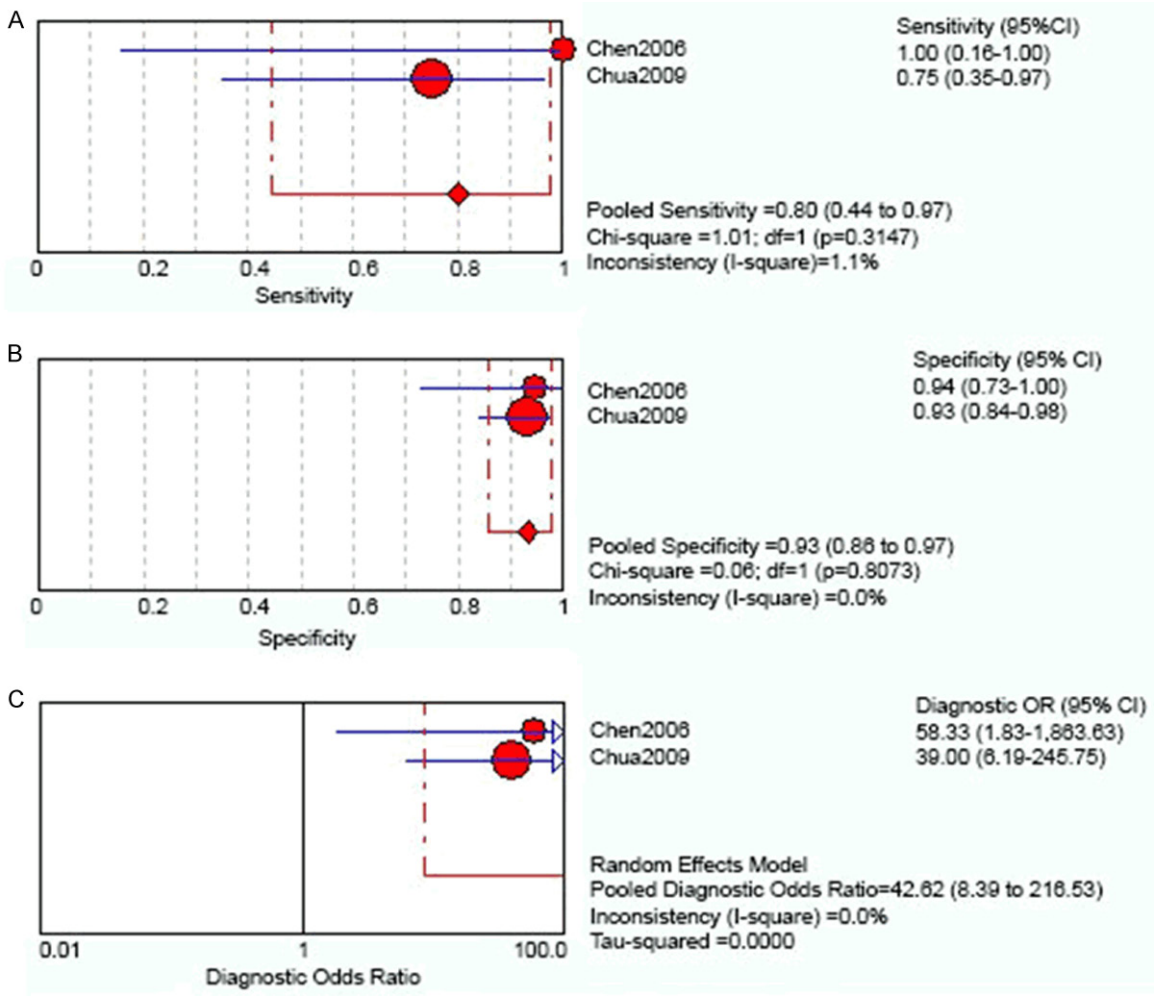

Figure 9. For M Classification by CT: A. Pooled sensitivity; B. Pooled specitficity; C. Pooled diagnostic odds ratio.

FDG PET/CT (0.88 (95% CI 0.85-0.90)). Moreover, sensitivity of MRI is equal to that of FDG PET/CT. Olmi study indicated that either CT or MRI can provide essential information in the staging of NPC. As regards to CT detection in N stage, only four studies were included while ten studies were included in MRI detection analysis and eleven studies included in FDG PET/CT analysis. Ng studied indicated that FDG PET/CT did not have adequate contrast resolution to identify the retropharyngeal nodes that merged with adjacent primary tumor or to discriminate direct tumor invasion from retropharyngeal metastasis. However for identifying cervical lymph node metastasis, FDG PET/CT may be more accurate than MRI [8]. The result of the analysis is keeping with King's study that FDG PET/CT and MRI had a similar diagnostic accuracy for neck lymph node staging [37].

In distant metastasis stage (M stage), Approximately 15% of untreated NPC patients shows distant metastasis at initial diagnosis [38]. In NPC patients, distant metastasis is generally investigated by conventional imaging work-up (chest X-ray, abdominal ultrasound, and bone scan). In this analysis, two studies reported diagnosis in NPC patients by whole-body MRI. The sensitivity of FDG PET/CT (0.82 (95% 0.74-0.88)) is higher than that of MRI (0.53 (95% CI 0.35-0.70)) and CT (0.80 (95% CI 0.44-0.97)), which is keeping with Senft study [39].

This analysis addresses a pragmatic question, incorporates recently published data including Chinese language and had a standardized study quality assessment. Sensitivity analysis showed consistent results to published review and suggested robustness of the findings.

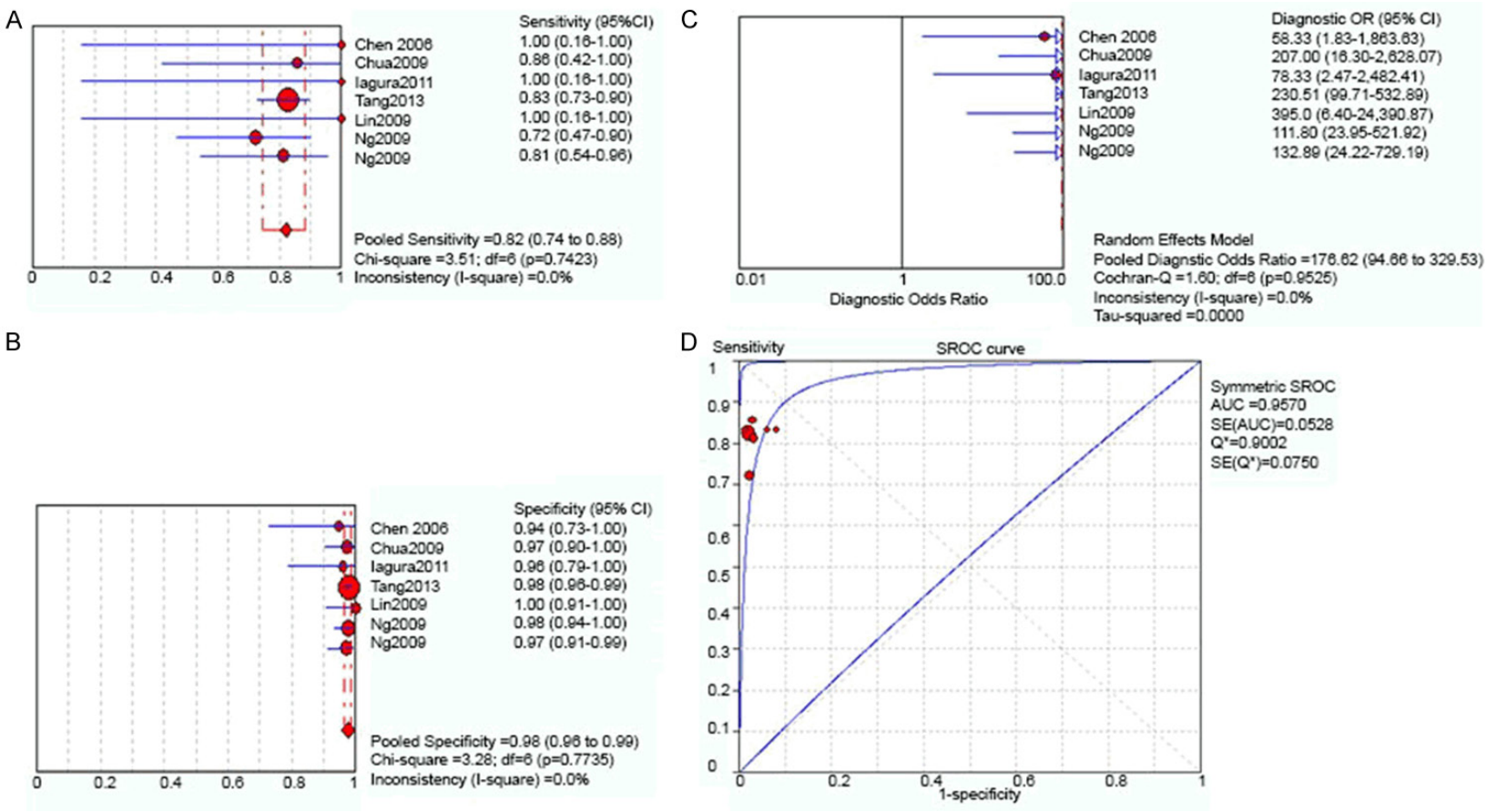

Figure 10. For M Classification by FDG PET/CT: A. Pooled sensitivity; B. Pooled specitficity; C. Pooled diagnostic odds ratio; D. Summary receiver operating Characteristic (SROC) curve with Q*-index.

There are some limitations of this meta-analysis. First of all, this analysis excluded the abstract, letter of editor. This may have cause to publication bias. Second, the reference standard in T NM staging and follow up time in M staging in the included studies were heterogeneity. This may influence the generalizability of the result. Thirdly, all the patients in the included studies in this analysis were pre-treated NPC. In residence and recurrence diagnosis of post-treated NPC patients, the scar or injury in lesion influences the diagnosis accuracy of MRI. These studies were excluded in this analysis. Lastly, even though the majority of the studies were of low-moderate risk of bias based on the QUADAS assessment, the designs in included studies were varied.

In conclusion, for newly pre-treat NPCMRI provides good accuracy in T staging. In N staging, CT showed more accuracy compared to MRI and FDG PET/CT. Based on the different of lymph node metastasis, MRI and FDG PET/CT can potentially aid the delineation. For M stage NPC patients, FDG PET/CT is routine investigations. Further research should be needed to investigate the accuracy of FDG PET/CT together with MRI as a single staging modality in NPC patients [40, 41].

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Disclosure of conflict of interest

None.

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