Research Article

Jianjiang Ruan, Yueqiao Zhang, Hong Ren*

Meta-analysis of PET/CT detect lymph nodes metastases of cervical cancer

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Abstract: Objective: The aim of this study was to assess the diagnostic value of PET/CT for metastatic lymph nodes in cervical cancer patients. Methods: Searching in the databases including PubMed, Embase, Web of Science, Cochrane Library and Google Scholar about non-invasive modalities for detecting lymph nodes metastases during 2000~2017. Following further screening, the extracted effective data were calculated by Meta-Disc 1.4 software, such as sensitivity (SEN), specificity (SPE), positive likelihood (LR+), and negative likelihood ratio (LR-). Results: we obtained 27 articles. The pooled estimates for sensitivity of PET/CT were 0.72 (95% CI, [0.69, 0.75]); for specificity were 0.96 (95% CI, [0.96, 0.97]). Its weighted AUC was 0.93. Conclusion: PET/CT remains to be an effective method for diagnosis of metastatic lymph nodes from cervical cancer.

Keywords: Lymph nodes metastases; PET/CT; Cervical cancer; Meta-analysis

1 Introduction

Cervical cancer is the second most common cancer in women all over the world. According to the statistics of the International Agency for Research on Cancer (IARC), the vast majority of new cases of cervical cancer worldwide each year are still in developing countries [1]. Because the survival rates of patients with lymph node metastasis are significantly lower than those without lymph node metastasis [2], an accurate detection of lymph node metastasis of cervical cancer is essential to ensure a proper treatment planning and prognosis for cervical cancer patients [3].

During the development of new radiotracers, the accuracy of Positron-emission tomography (PET) imaging has improved, particularly for antibody-targeted imaging. The oncologists have paid an attention to the field of diagnosis of metastatic lymph nodes by using PET. The principle of PET imaging is that the radioisotopes and other positron-specific radionuclide-labeled basic metabolic substrate accumulate in the lesion, detecting these particular radiation to determine metabolism of lesions. The F18-deoxyglucose is a common radio-labeled drug, which has the characteristics of small radiation, decay fast. F18-deoxyglucose may be injected into a patient, taken up preferentially by abnormal oncologic tissue, and measured using a PET scanner [4]. PET/CT with the advantages of molecular imaging techniques, anatomical and functional characteristics and confirmed diagnostic value in all kinds of solid tumors, PET/CT has been applied in the initial stages of cervical cancer patients, treatment planning, testing and follow-up after treatment and prognostic judgement [5]. In order to objectively evaluate a diagnostic value of PET/CT on lymph node metastasis of cervical cancer, we analyzed the quality of PET/CT in the diagnosis of cervical lymph node metastasis by using systematic review method.

2 Methods

2.1 Searching method

We conducted a search of PubMed, Embase, Web of Science, Cochrane Library and Google Scholar databases that were published between 2000 and 2017. We limited the search to study published in English. The medical subject heading terms and keywords used included “lymph node”, “PET/CT”, “sensitivity”, “specificity”, “accuracy”, and “diagnostic value”. Duplicate articles

***Corresponding author: Hong Ren,** Department of Radiology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou 310016, China, E-mail address: renhongzj@126.com
Jianjiang Ruan, Department of Radiology, Shaoxing Shangyu Women and Children Hospital, Zhejiang 312300, China.
Yueqiao Zhang, Department of Radiology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou 310016, China.

and unpublished studies from international meetings were excluded. The flow diagram of the retrieval process is shown in Figure 1.

2.2 Inclusion criteria

Studies were selected carefully on the basis of following criteria: The pathology results as "gold standard", lymph nodes metastases were confirmed by surgery or biopsy; the diagnostic criteria were clear; a case control study (there are 2×2 contingency tables); direct or indirect access to true positive, false positive, false negative, true negative, sensitivity, specificity.

2.3 Excluding standard

Non-clinical controlled trials; lack of confirmed evidence by pathological examination; Incomplete data; Case reports; Review literature; Data published repeatedly.

2.4 Data extraction

Two authors independently assessed each literature, and then downloaded and extracted all the data by using standardized data-abstraction forms. The data extracted included year of publication, true positive, false positive, false negative, true negative, sensitivity, and specificity. For each study, 2×2 contingency tables were constructed.

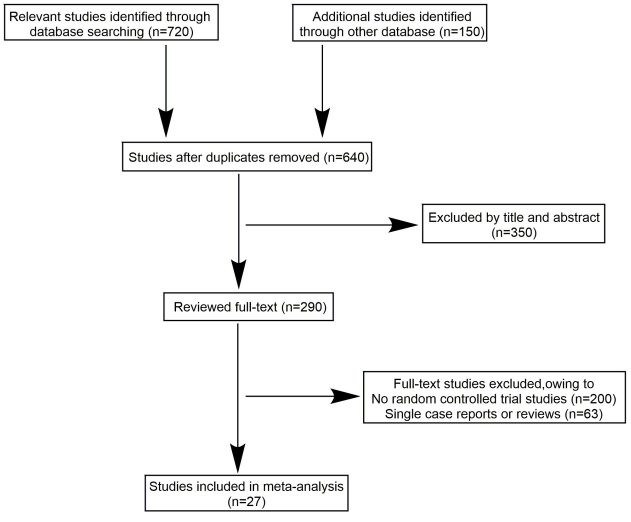


Figure 1: The study selection process

We calculated the sensitivity, specificity, and likelihood ratio (LR).

2.5 Statistical analysis

The sensitivity, specificity and 95% confidence interval (CI) of the literature were analyzed by Meta-disc 1.4 software, and the summary receiver operating characteristic (SROC) curves and forest map were drawn. According to the results of heterogeneity test, the corresponding fixed effect model or the random effect model is selected to quantify the effect values.

3 Results

3.1 Literature search and characteristics of eligible study

According to search strategy, 27 full articles were finally considered eligible for the review after evaluation. Figure 1 shows the flow diagram of study selection process. The detailed characteristics for the 27 eligible studies are summarized in Table 1.

3.2 Quality assessment

We assessed the quality of included studies according to QUADAS. Each study was respectively evaluated by two independent investigators. On average, the investigators disagreed on 3 of 11 items (range, 0–6). All disagreements were resolved by consensus.

3.3 The diagnostic sensitivity and specificity of PET/CT

The pooled diagnostic sensitivity and specificity of PET/CT are 0.72 (95% CI, [0.69, 0.75]), 0.96 (95% CI, [0.96, 0.97]), respectively. Significant heterogeneity was found among these studies (I^2=88.6% and 93.0%). Due to significant heterogeneity of the data, we used a random effects model (Figure 2 and 3).

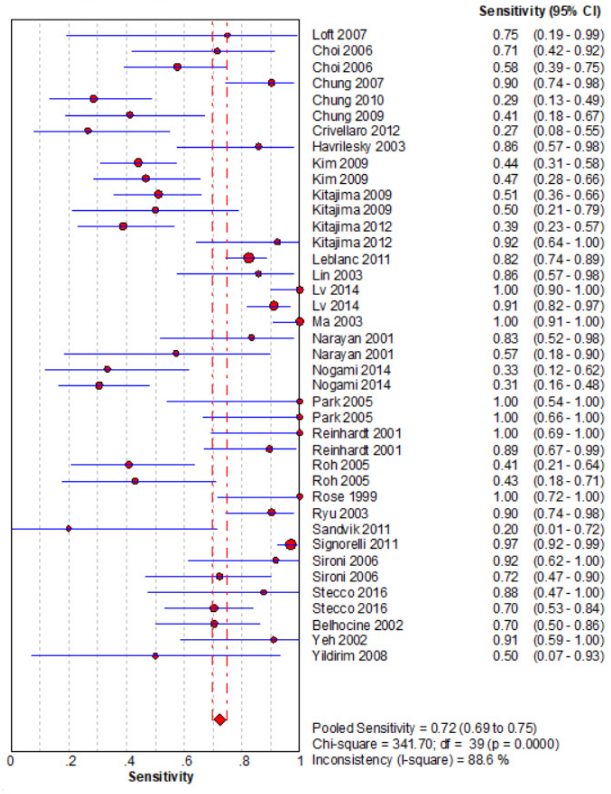


Figure 2: The plot for the sensitivity of PET/CT

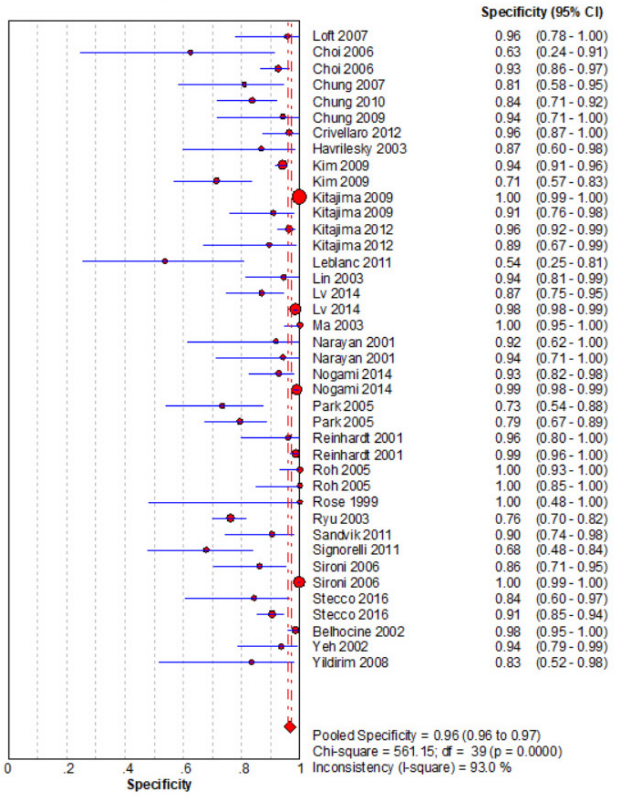


Figure 3: The plot for the specificity of PET/CT

3.4 The negative LR, positive LR and SROC curve of PET/CT

The pooled negative LR and positive LR of PET/CT are 0.34 (95% CI, [0.27, 0.44]), 9.12 (95% CI, [6.19, 13.45]), respectively (Figure 4 and 5). We successfully plotted the SROC curve. The area under the SROC curve (AUC) is 0.93 and the Q* is 0.86 (Figure 6).

3.5 Subgroup analysis

Subgroup analysis showed that the performance of PET/CT in detecting the lymph nodes metastases in patient-based unit, the pooled diagnostic sensitivity and specificity are 0.80 (95% CI, [0.76, 0.83]), 0.87 (95% CI, [0.84, 0.89]), respectively. In region-based unit, the pooled diagnostic sensitivity and specificity are 0.64 (95% CI, [0.60, 0.68]), 0.98 (95% CI, [0.98, 0.98]), respectively. Meta-analysis results are shown in Table 2.

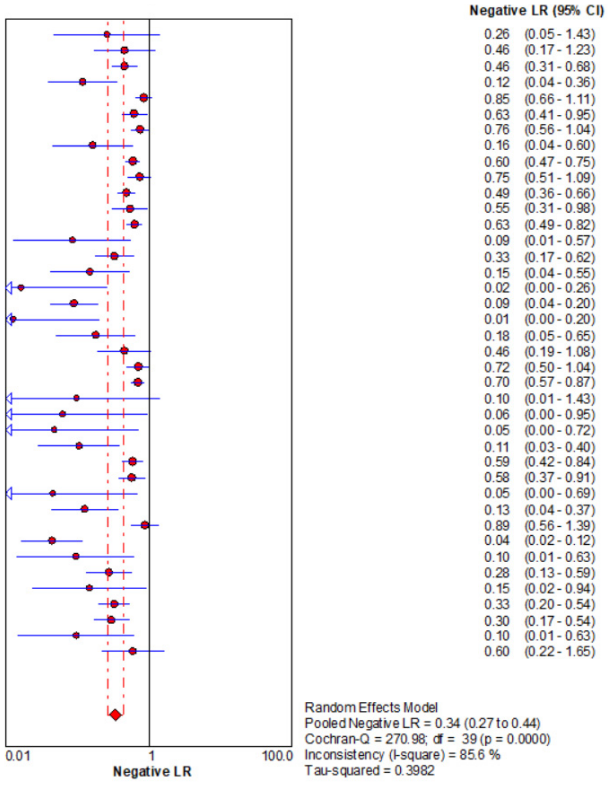
4 Discussion

Cervical cancer is the third most common malignant tumor in women worldwide after breast cancer and colorectal cancer. With younger onset age, the increase of its incidence and recurrence rate after treatment, cervical cancer becomes significantly more influential on women's health. Thus, a diagnosis of lymph node metastasis as early as possible has an important clinical significance. This systematic review included 27 studies of PET/CT for the diagnosis of cervical lymph node metastasis with surgical pathology as a reference standard. The data showed that the diagnosis of cervical lymph node metastasis with moderate sensitivity and specificity can be used as one of the effective diagnostic methods of cervical lymph node metastasis.

To reduce heterogeneity, we performed a subgroup analysis. The result of subgroup analysis showed that the patient-based analysis unit had a higher sensitivity than the lymph node analysis unit, suggesting that cervical lymph node metastasis of suspected cases can be effectively screened when PET/CT diagnosis is positive. The lymph node as the unit of analysis compared with the patient as the unit of analysis has a higher specificity,

Table 1: Baseline characteristics of included studies

Studies	Comparisons	Sample	Metastatic positions	TP	FP	FN	TN	SEN	SPE
Loft 2007(6)	R	27	Pelvic	3	1	1	22	75	95.7
Choi 2006(7)	P	22	Pelvic, Para-aortic	10	3	4	5	71.4	62.5
Choi 2006(7)	R	154	Pelvic, Para-aortic	19	9	14	112	57.6	92.6
Chung 2007(8)	P	52	Pelvic	28	4	3	17	90.3	81.0
Chung 2010(9)	P	83	Pelvic	8	9	20	46	28.6	83.6
Chung 2009(2)	P	34	Pelvic	7	1	10	16	41.2	94.1
Crivellaro 2012(10)	P	69	Pelvic	4	2	11	52	26.7	96.3
Havrilesky 2003(11)	P	29	Para-aortic	12	2	2	13	85.7	86.7
Kim 2009(12)	R	553	Pelvic, Para-aortic	26	30	33	464	44.1	93.9
Kim 2009(12)	P	79	Pelvic, Para-aortic	14	14	16	35	46.7	71.4
Kitajima 2009(13)	R	1976	Pelvic, Para-aortic	23	4	22	1927	51.1	99.8
Kitajima 2009(13)	P	45	Pelvic, Para-aortic	6	3	6	30	50.0	90.9
Kitajima 2012(14)	R	200	Pelvic, Para-aortic	14	6	22	158	38.9	96.3
Kitajima 2012(14)	P	32	Pelvic	12	2	1	17	92.3	89.5
Leblanc 2011(15)	R	132	Para-aortic	98	6	21	7	82.4	53.8
Lin 2003(16)	P	50	Pelvic, Para-aortic	12	2	2	34	85.7	94.4
Lv 2014(17)	P	87	Pelvic, Para-aortic	34	7	0	46	100	86.8
Lv 2014(17)	R	1163	Pelvic, Para-aortic	61	17	6	1079	91	98.4
Ma 2003(18)	P	104	Pelvic, Para-aortic	38	0	0	66	100	100
Narayan 2001(19)	P	24	Pelvic, Para-aortic	10	1	2	11	83.3	91.7
Narayan 2001(19)	R	24	Pelvic, Para-aortic	4	1	3	16	57.1	94.1
Nogami 2014(20)	R	70	Pelvic, Para-aortic	5	4	10	51	33.3	92.7
Nogami 2014(20)	R	848	Pelvic, Para-aortic	11	9	25	803	30.6	98.9
Park 2005(21)	P	36	Pelvic	6	8	0	22	100	73.3
Park 2005(21)	R	72	Pelvic	9	13	0	50	100	79.4
Reinhardt 2001(22)	P	35	Pelvic	10	1	0	24	100	96
Reinhardt 2001(22)	R	292	Pelvic	17	4	2	269	89.5	98.5
Roh 2005(23)	R	72	Pelvic	9	0	13	50	40.9	100
Roh 2005(23)	P	36	Pelvic	6	0	8	22	42.9	100
Rose 1999(24)	P	16	Para-aortic	11	0	0	5	100	100
Ryu 2003(25)	P	249	Para-aortic	28	52	3	166	90.3	76.1
Sandvik 2011(26)	P	36	Pelvic	1	3	4	28	20.0	90.3
Signorelli 2011(27)	P	159	Pelvic	127	9	4	19	96.9	67.9
Sironi 2006(28)	P	48	Pelvic, Para-aortic	11	5	1	31	91.7	86.1
Sironi 2006(28)	R	1081	Pelvic	13	3	5	1060	72.2	99.7
Stecco 2016(29)	P	27	Pelvic	7	3	1	16	87.5	84.2
Stecco 2016(29)	R	216	Pelvic	26	17	11	162	70.3	90.5
Belhocine 2002(30)	P	217	Pelvic, Para-aortic	19	3	8	187	70.4	98.4
Yeh 2002(31)	P	42	Pelvic	10	2	1	29	90.9	93.5
Yildirim 2008(32)	R	16	Pelvic	2	2	2	10	50.0	83.3



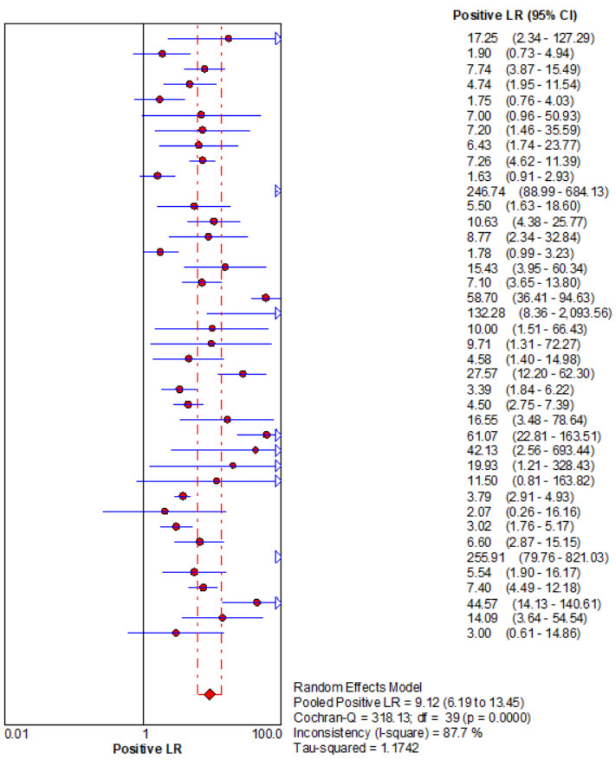


Figure 4: The plot for the negative LR of PET/CT

Figure 5: The plot for the positive LR of PET/CT

Table 2: Subgroup analysis of pooled sensitivity, specificity, likelihood ratio

Subgroup	SEN (95%CI)	SPE (95%CI)	+LR (95%CI)	-LR (95%CI)
Analysis units				
Patient-based (n=24)	0.80(0.76-0.83)	0.87(0.84-0.89)	5.62(3.84-8.22)	0.24(0.15-0.39)
Region-specific (n=16)	0.64(0.60-0.68)	0.98(0.98-0.98)	15.60(7.73-31.48)	0.43(0.33-0.56)
Metastatic positions				
Pelvic (n=19)	0.76(0.71-0.80)	0.96(0.95-0.97)	8.36(4.92-14.18)	0.31(0.20-0.48)
Para-aortic (n=4)	0.85(0.79-0.90)	0.76(0.70-0.81)	3.33(1.85-5.98)	0.18(0.08-0.42)
Pelvic and Para-aortic (n=17)	0.65(0.60-0.69)	0.98(0.97-0.98)	12.03(6.20-23.37)	0.40(0.29-0.55)

likelihood ratio, the negative likelihood ratio, indicating that it can effectively rule out cases of cervical lymph node metastasis when the PET/CT diagnosis is negative.

The quality of results evaluated in this systematic review proved to be insubstantial. Due to the low quality research and literature included being based mostly on the retrospective studies, there may be inherent choice bias. There was a large heterogeneity in this study. The combined analysis showed that I^2 was more than 50%, the reason may be due to inconsistencies in criteria of interpretation of PET/CT. In the process of literature filtering we found: (1) most of the research in measuring results without using the blind method. Possible interpretation bias; (2) most of the literature does not report the sensitivity and specificity; these problems will inevitably affect the quality of the literature and combined analysis.

In summary, PET/CT in the diagnosis of pelvic lymph node metastasis in cervical cancer ability has a moderate sensitivity and high specificity. The results will help

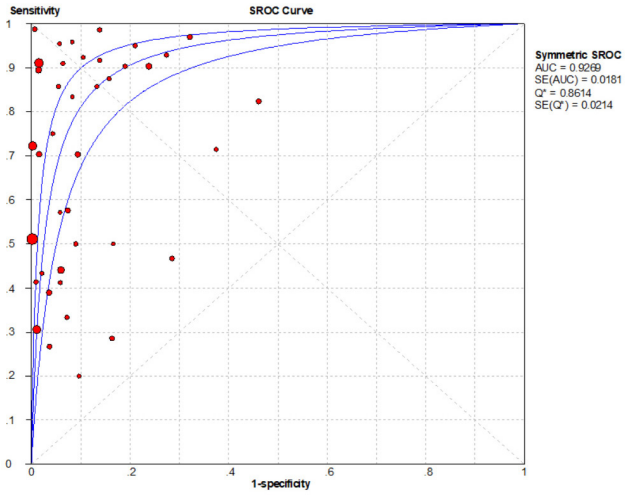


Figure 6: The SROC curve of PET/CT

us to accurately evaluate the preoperative cervical cancer patients.

Conflict of interest: No conflicts of interest to disclose.

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