Systematic Review and Meta-Analysis

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Direct comparison of choline PET/CT and MRI in the diagnosis of lymph node metastases in patients with prostate cancer

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Abstract

Background: Lymph node detection in prostate cancer is challenging and critical to determine treatment policy. Choline PET/CT (positron emission tomography/computed tomography) and magnetic resonance imaging (MRI) have been used for the evaluation of lymph node metastasis in patients with prostate cancer for the past decade. However, only limited patients underwent direct comparison studies.

Purpose: To evaluate the diagnostic performance of choline PET/CT compared with MRI imaging for detecting lymph node metastases in prostate cancer patients.

Material and Methods: Relevant English-language articles published before February 2018 were searched in PubMed database, Embase database, and Cochrane Library databases search using the keywords: (Prostate Neoplasm OR Prostate Cancer OR prostate carcinoma) and (Lymph Node) and (PET/CT OR positron emission tomography/computed tomography) and (choline or 2-hydroxy-*N*,*N*,*N*-trimethylethanaminium) and (magnetic resonance imaging OR MRI). Articles were included that directly compare the diagnostic performance and clinical utility of choline PET/CT and MRI for detecting lymph node metastases in prostate cancer patients. Study quality was assessed with QUADAS criteria. Analyses were performed on a per patient and a per node basis. The pooled sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (LR+), and negative likelihood ratio (LR−) were calculated using Meta-Disc 1.4 software. Summary receiver-operating characteristic (SROC) curves constructed.

Results: A total of 362 patients from 8 studies involving fulfilled the inclusion criteria. On patient-based analysis, the pooled sensitivity, specificity, and DOR with a 95% confidence interval (CI) for choline PET/CT imaging were 0.59 (95%CI, 0.50–0.67), 0.92 (95%CI, 0.87–0.96), 17.37 (95%CI, 4.42–68.33), and for MRI imaging, they were 0.52 (95%CI, 0.44–0.61), 0.87 (95%CI, 0.81–0.92), 6.05 (95%CI, 3.09–11.85), respectively. On node-based, the corresponding values for choline PET/CT imaging were 0.51 (95%CI, 0.46–0.57), 0.99 (95%CI, 0.98–0.99), 65.55 (95%CI, 23.55–182.45), and for MRI imaging, they were 0.39 (95%CI, 0.34–0.44), 0.97 (95%CI, 0.96–0.97), 15.86 (95%CI, 8.96–28.05), respectively.

Conclusion: Choline PET/CT performed better than MRI imaging in evaluating the lymph nodes metastasis of prostate cancer patients and had the potential to be broadly applied in clinical practice.

Abbreviations: ^{18}F-FDG = ^{18}F-fluorodeoxyglucose, AUC = area under the curve, CI = confidence interval, CT = computed tomography, DOR = diagnostic odds ratio, FN = false negative, FP = false positive, LND = lymph node dissection, LR− = negative likelihood ratio, LR+ = positive likelihood ratio, MRI = magnetic resonance imaging, PCa = prostate cancer, PET/CT = positron emission tomography / computed tomography, QUADA = diagnostic accuracy studies, SROC = summary receiver-operating characteristic, TN = true negative, TP = true positive.

Keywords: choline, lymph node, MRI, PET/CT, prostate cancer

1. Introduction

Prostate cancer (PCa) is the highest prevalence of cancer in men (180,890 cases, 21% of all new tumor cases) and the third leading cause of cancer-associated death (26,120 cases, 8% of the total deaths).[1,2] The most common metastatic site of PCa is regional lymph nodes.[3] The definition of lymph node metastases extent in PCa has important implications not only for the prognosis of patients but also for the decision-making process.[4] Lymph node metastasis is correlated with progressive disease in most PCa patients, and the 5-year disease-free survival rate is 85% in nonmetastatic patients.[5] But for patients with lymph node metastasis, survival rate is reduced to <50%, and the more lymph nodes metastasis, the worse the survival potentia.[5] PCa recurrence after primary treatment depends on initial tumor stages. Therefore, invasive and more reliable diagnostic methods of staging and restaging are particularly desirable.

Radiologic imaging plays an important role in the restaging of PCa.[6] Several imaging techniques have been used to detect

Editor: Saad Zakko.

Funding: This work was supported by funding from Basic research project of Logistics University of Chinese People's Armed Police Forces (WHJ201725).

The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:50(e13344)

Received: 27 August 2018 / Accepted: 27 October 2018

http://dx.doi.org/10.1097/MD.0000000000013344

lymph node metastasis of PCa, such as computed tomography (CT) and ultrasound. However, CT and ultrasound do not provide high diagnostic accuracy in detecting lymph node metastasis.[7,8] In a cohort of more than 1500 PCa patients undergoing preoperative CT scan, radical prostatectomy and lymph node dissection at a single center, the sensitivity of CT scan as a preoperative nodal-staging was only 13%.[8] At present, magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) are the most promising tools. Molecular imaging technique PET/CT, which combines the metabolic activity depicted by PET with the tissue anatomical structure by CT, can provide more diagnostic information in a single diagnostic session using a single device. Also the tracer choice is very important for PET/CT imaging, ^{18}F-fluorodeoxyglucose (^{18}F-FDG), is the most commonly used radiopharmaceutical for PET/CT in clinical. ^{18}F-FDG uptake in metastatic PCa has been shown to correlate with tumor aggressiveness and grade. However, well-differentiated PCa has lower levels of glucose metabolism than other tumors types, and ^{18}F-FDG is normally highly concentrated in the urine. In addition, pelvic pathology can be obscured or mimicked by urinary radiotracer activity (particularly in thin patients).

Among a variety of PET/CT radiotracers that have been used for PCa, ^{11}C-choline or ^{18}F-choline have been emerged as a promising molecular imaging tool to provide a body examination for PCa at present. The European Urology Association updated guidelines on PCa in 2016, stating the importance of PET with choline combined with CT to identify lymph node involvement and metastatic spread at all stages.[9] The fundamental of choline as a tracer labeled with ^{11}C or ^{18}F is that choline, as a precursor for the synthesis of phospholipids, is part of the cell membrane, whereby the upregulated of the key enzyme choline kinase in PCa cells leads to an increase in the demand for substrate (choline). Moreover, PCa cells show an upregulated transport rate with an increased expression of choline transporters. A major advantage of choline is its rapid uptake within prostate tissue (3–5 minutes) and rapid blood clearance (5 minutes).[6] This allows for early imaging prior to excretion of the radiotracer into the urine. Thus, the pelvis can be viewed before significant excretory activity becomes a potential confounder. Many researchers have used choline PET/CT for restaging PCa, especially for detecting distant metastases of lymph node. However, some different studies reported the diagnostic accuracy of the choline PET/CT imaging and MRI detecting lymph node metastasis in PCa patients is still controversial.[10–14] Notably, so far, no direct comparison of the diagnostic value between MRI with choline PET/CT in meta-analysis has been published.

The purpose of our meta-analysis of original research studies was to directly compare the diagnostic performance and clinical utility of choline PET/CT and MRI for detecting lymph node metastases in PCa patients.

2. Material and methods

2.1. Literature search

In the medical database PubMed, Embase, and Cochrane Library databases with no language restriction from inception to February 2018), we conducted a systematic search about studies in human subjects were performed to evaluate the diagnostic performance of choline PET/CT compared with MRI imaging for detecting lymph node metastases in PCa patients. We performed an extensive search filter by using the following search terms and Boolean logic words: (prostate neoplasm OR prostate cancer OR prostate carcinoma) and (lymph node) and (PET/CT OR positron emission tomography/computed tomography) and (choline or 2-hydroxy-*N*,*N*,*N*-trimethylethanaminium) and (magnetic resonance imaging OR MRI). In order to supplement the database searches, we reviewed the references of relevant review articles and eligible studies.

2.2. Inclusion and exclusion criteria

Two observers evaluated the title and abstracts independently. From the retrieved articles via our systematic search, we removed duplicates by using the Endnote X7 software and further examined full-text articles of potentially eligible citations. To solve the disagreements through mutual discussion, studies were included in the systematic review if the numbers of true positive (TP), false positive (FP), false negative (FN), and true negative (TN) test results were provided by the articles, which make the 2×2 contingency tables available; direct comparison of choline PET/CT and MRI in the diagnosis accuracy of lymph node metastases in PCa patients; use of histological examination with or without clinical follow-up as the reference standard to evaluate diagnostic performance; and at least 8 patients included.

We excluded studies that only evaluate the diagnostic performance of choline PET/CT or MRI in the diagnosis of lymph node metastases and without adequate information to allow construct 2×2 contingency tables. Review articles, conference abstract, preclinical studies, case reports, errata, and studies including $\leq$ 8 patients were excluded.

2.3. Study quality assessment

The Quality Assessment of Studies of Diagnostic Accuracy Studies (QUADA)[15] based on a 14-point scale was used to evaluate the quality of the 8 included studies. This quality assessment tool is produced to evaluate the quality of diagnostic accuracy studies in systematic reviews. The tool consists of 4 key domains and 7 aspects, with respect to risk of bias and concern about applicability of patient selection, index test, reference standard, and the bias risk of flow and timing. Each item of the QUADA checklists were answered with yes, no or unclear. An answer of "yes" gets one score, which means low risk of bias, whereas an answer of "no" or "unclear" gains a score of "0" which suggests that a high risk of bias may exist.

The 2 independent reviewers evaluate the quality of the 8 studies. Inconsistent findings between the 2 reviewers were solved by discussion, and thus the final report was agreed upon by consensus.

2.4. Data extraction

For each included study, 2 reviewers independently used a standardized spreadsheet to extract the following relevant information: first author's surname, year of publication, method, patient demographic (the number of included patients who underwent PET/CT and MRI for the assessment of lymph node metastasis, age, sex), technical specifications of PET/CT and MRI, PET/CT and MRI results (TP, FP, FN, TN based on patients or lymph nodes).

2.5. Statistical analysis

All analyses were calculated based on 2 types of comparison method with statistical software MetaDisc version1.4 (Unit of

Clinical Biostatistics, Ramo'n y Cajal Hospital, Madrid, Spain); one is patient-based analysis, and the other is node-based analysis.

A patient-based data analysis uses the pathologically proven positive node in the same patient who had been identified to have metastatic lymph nodes by preoperative imaging, while node-based date analyses use the pathologically proven positive node in the corresponding node which had been described as containing positive node by preoperative imaging.

The pooled sensitivity, specificity, positive likelihood ratio (LR +), negative likelihood ratio (NL-), diagnostic odds ratio (DOR) with the respective 95% confidence intervals (95% CI) were calculated of each imaging technology. We also calculated summary receiver operating characteristics curves (SROC) and the area under the curve (AUC) to assess the interaction between sensitivity and specificity.

Finally, a 2-sample *Z*-test was performed to evaluate a significant difference in sensitivity, specificity, DOR, AUC or the Q^* index between these 2 techniques. A *P* value <.05 was considered to be statistically significant. All of the statistical analyses were performed using Meta-DiSc version 1.4[16] or SPSS 13.0 (SPSS Inc., Chicago, IL).

The *I*-square (I^2) tests was used to evaluate the statistical heterogeneity. It was considered significant study heterogeneity if the I^2 value was >50%. When the I^2 value was >50%, the pooled estimates were carried out by random-effects model, otherwise performed by fixed-effects model for the meta-analysis.

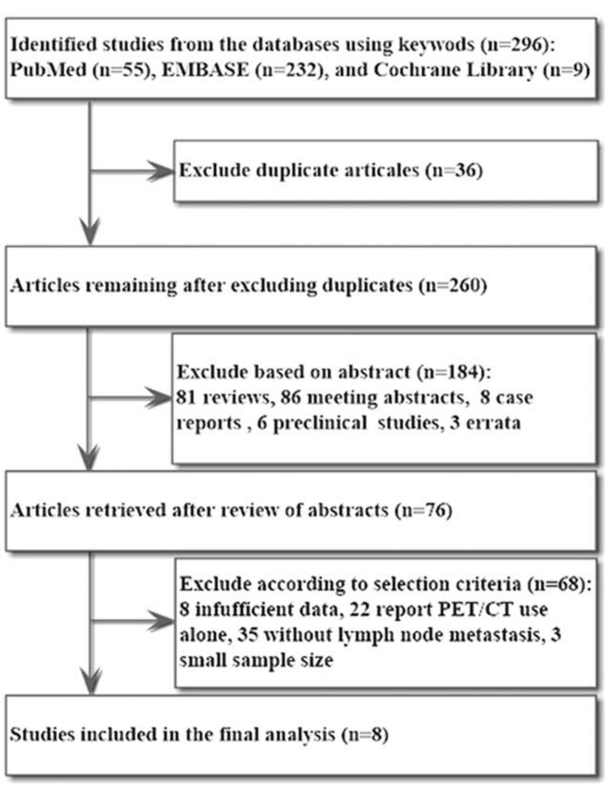

Figure 1. Flow diagram of selected studies for the accuracies of choline PET/CT and MRI for detecting lymph node metastases in prostate cancer patients. MRI = magnetic resonance imaging, PET/CT = positron emission tomography/computed tomography.

3. Results

3.1. Study selection and characteristics

After the systematic search using the keywords and extensive review the references of relevant articles, we initially identified 296 studies in total. After exclusion duplicates (n = 260), we reviewed the title and abstract of the remaining articles, and 81 review articles, 86 meeting abstracts, 8 case reports, 6 preclinical studies, and 3 errata were exclusion. We reviewed the remaining 76 articles, 8 studies[17–24] remained after applying the inclusion and exclusion criteria. The whole process of the literature search was shown in Figure 1.

The studies of included comprising 362 patients, with the average age 66.2. The included studies were reported from different countries, of those, 2 studies were performed 2 in Belgium, 2 in Germany, 1 in America,1 in United Kingdom, 1 in Italy, and 1 in France. All the included studies were conducted prospectively design. Six studies used ^{11}C-choline as the radiotracer, and PET/CT scanning started between 2 and 5 minutes after intravenous injection with ^{11}C-choline an additional low-dose CT in 10 studies. Whereas 2 studies used ^{18}F-choline and PET/CT scanning started 60 minutes after intravenous injection with ^{18}F-choline. The study populations and their characteristics of the 8 studies were summarized in Table 1.

3.2. Quality assessment

Quality assessment is showed in Table 2 using the QUADAS 2 tool consisting of 14 items, including representative spectrum of patients (item 1), selection criteria (item 2), reference standard (item 3), the time of between reference standard and index test (item 4), using a reference standard of diagnosis (item 5), receive the same reference standard (item 6), reference standard independent of the index test (item 7), execution of the index test described (item 8), execution of the reference standard described (item 9), index test results interpreted (item 10), reference standard results interpreted (item 11), clinical data available (item 12), uninterpretable/ intermediate test results reported (item 13), withdrawals from the study explained (item 14). The results are showed in Table 2.

3.3. Summary of diagnostic accuracy

3.3.1. Patient-based data analysis. Table 3 presents the performance of PET/CT and MRI for the detection of lymph node metastases from each study and the results of the statistical pooling, based on the patient-based data analysis. The pooled sensitivity, specificity, LR+, LR−, and DOR of PET/CT were 0.59 (95%CI, 0.50–0.67), 0.92 (95%CI, 0.87–0.96), 5.45 (95%CI, 2.65–11.22), 0.38 (95%CI, 0.19–0.76) and 17.37 (95%CI, 4.42–68.33), respectively, and those of MRI were 0.52 (95%CI, 0.44–0.61), 0.87 (95%CI, 0.81–0.92), 3.29 (95%CI, 2.08–5.22), 0.62 (95%CI, 0.50–0.77) and 6.05 (95%CI, 3.09–11.85), respectively. The specificity, LR+, LR− and DOR of PET/CT were significantly higher than those of MRI ($P < .05$). The SROC curves are presents in Figures 2 and 3. The AUC and Q^* index of PET/CT were 0.9526 and 08940, respectively, and those values of MRI were 0.7782 and 0.7170, respectively. The AUC and Q^* index of PET/CT were higher than those of MRI ($P < .05$).

3.3.2. Node-based data analysis. Table 3 presents the performance of PET/CT and MRI for detection of lymph node

Table 1

Characteristics of included studies.

Study (publication year)	Countries	Patients	Lymph nodes	Mean age	Study design	PET/CT	Radiotracer doses	Uptake interval (min) after injection	MRI	Reference standard
Budiharto T 2011	Belgium	36	733	64.6	Prospectively	Siemens	740–1000 MBq ^{11}C-choline	2	Siemens	HP
Heck MM 2013	Germany	33	261	66.0	Prospectively	Siemens	756±72 MBq ^{11}C-choline	5	Siemens	HP
Wieder H 2017	Germany	57	456	68.0	Prospectively	GE	600–900 MBq ^{11}C-choline	5	Siemens	HP
Kitajima K 2014	America	70	122	65.7	Prospectively	GE	370–555 MBq ^{11}C-choline	5	GE	HP, CFU
Contractor K 2011	UK	26	406	67.7	Prospectively	GE	Unclear ^{11}C-choline	Unclear	Phillips	HP
Piccardo A 2014	Italy	21	55	77.2	Prospectively	GE	3 MBq/kg ^{11}F-choline	Unclear	GE	HP, CFU
Pinaquy JB 2014	France	44	482	63.0	Prospectively	GE	4 MBq/kg ^{18}F-choline	60	Phillips	HP
Van den Bergh L 2015	Belgium	75	1665	64.6	Prospectively	Siemens	740–1000 MBq ^{11}C-choline	4	Siemens	HP

CFU = clinical follow-up, HP = histopathology, MRI = Magnetic resonance imaging, PET/CT = positron emission tomography/computed tomography.

Table 2

Quality assessment of study using the QUADAS tool.

Study	Item 1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total score
Budiharto T	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13
Heck MM	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	12
Wieder H	Y	Y	Y	Y	N	Y	Y	Y	U	Y	Y	Y	Y	Y	12
Kitajima K	Y	Y	Y	U	Y	N	Y	Y	Y	Y	U	Y	Y	Y	11
Contractor K	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	12
Piccardo A	Y	Y	Y	Y	Y	N	Y	N	Y	U	U	Y	Y	Y	10
Pinaquy JB	U	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	11
Van den Bergh L	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13

Y, yes = 1 score, N, no = 0 score, U, unclear = 0 score.

metastases from each study and the results of the statistical pooling, based on the node-based data analysis. The pooled sensitivity, specificity, LR+, LR− and DOR of PET/CT were 0.51 (95%CI, 0.46–0.57), 0.99 (95%CI, 0.98–0.99), 23.73 (95%CI, 12.65–44.52), 0.42 (95%CI, 0.24–0.75) and 65.55 (95%CI, 23.55–182.45), respectively, and those of MRI were 0.39 (95% CI, 0.34–0.44), 0.97 (95%CI, 0.96–0.97), 8.31 (95%CI, 6.48–10.64), 0.61 (95%CI, 0.45–0.82) and 15.86 (95%CI, 8.96–28.05), respectively. The sensitivity, LR+, LR−, and DOR of PET/CT were significantly higher than those of MRI ($P < .05$). The SROC curves are shown in Figures 4 and 5. The AUC and Q^* index of PET/CT were 0.9857 and 0.9485, respectively, and those values of MRI were 0.9331 and 0.8689, respectively. The AUC and Q^* index of PET/CT were higher than those of MRI ($P < .05$).

4. Discussion

Management of PCa patients strongly depends on accurate initial assessment of the tumor stage (T), the absence or the presence of lymph node involvement (N), and the absence or the presence of nonregional metastases (M), both in primary staging and restaging. Early clinical symptoms of PCa is not very significant, the biological characteristics of PCa is more complicated. Clinically, most of the patients with PCa are advanced stage of treatment, some have distant metastasis. Although the 10-year survival rate of early stage PCa is high, the prognosis is generally poor in the case of metastasis.[25] Studies have shown that about 25% to 41% of patients with PCa have developed lymph node metastases, and the smallest metastasis only 2 mm.[26] Pelvic lymph nodes are the earliest and most common site of PCa metastasis. Patients with positive lymph node metastases have

Table 3

Pair-wise comparisons between PET/CT and MRI for sensitivity, specificity, LR+, LR−, DOR, AUC, and Q^* values by patient-based data or node-based data.

Study	SEN (95%CI)	SPE (95%CI)	LR+ (95%CI)	LR− (95%CI)	DOR (95%CI)	AUC	Q^*
Patient-based							
PET/CT	0.59 (0.50–0.67)	0.92 (0.87–0.96)	5.45 (2.65–11.22)	0.38 (0.19–0.76)	17.37 (4.42–68.33)	0.9526	0.8940
MRI	0.52 (0.44–0.61)	0.87 (0.81–0.92)	3.29 (2.08–5.22)	0.62 (0.50–0.77)	6.05 (3.09–11.85)	0.7782	0.7170
Node-based							
PET/CT	0.51 (0.46–0.57),	0.99 (0.98–0.99)	23.73 (12.65–44.52)	0.42 (0.24–0.75)	65.55 (23.55–182.45)	0.9857	0.9485
MRI	0.39 (0.34–0.44)	0.97 (0.96–0.97)	8.31 (6.48–10.64)	0.61 (0.45–0.82)	15.86 (8.96–28.05)	0.9331	0.8689

The following comparisons were no statistically significant differences: PET/CT versus MRI for pooled sensitivity by patient-based data and PET/CT versus MRI for pooled specificity by node-based data. DOR = diagnostic odds ratio, LR+ = positive likelihood ratio, MRI = magnetic resonance imaging, NL− = negative likelihood ratio, PET/CT = positron emission tomography/computed tomography, SEN = sensitivity; SPE: specificity.

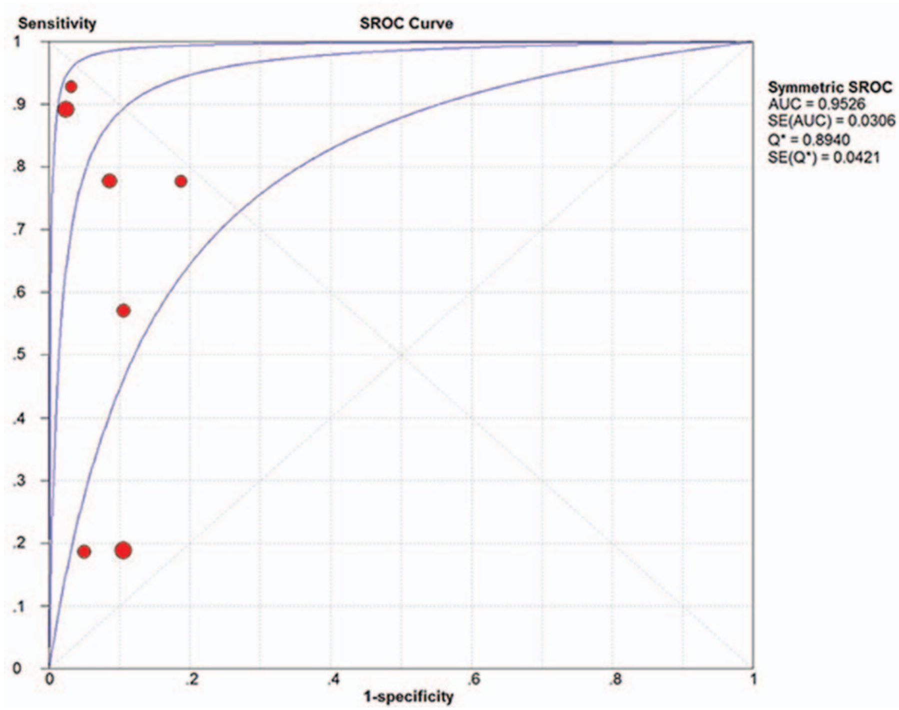

Figure 2. Summary receiver operating characteristic curve showing the performance of choline PET/CT for detecting lymph node metastases in prostate cancer patients on patient-based analysis. PET/CT = positron emission tomography/computed tomography.

poor survival, and patients in this disease category were considered incurable.[27]

Currently, the treatment options for PCa patients include radical prostatectomy, radiotherapy, chemotherapy, endocrine therapy, observation waiting, or a combination of these, and the selection of PCa treatment options needs to be based on the clinical staging of patients to maximize treatment efficacy and reduce treatment morbidity. The most effective treatment for PCa

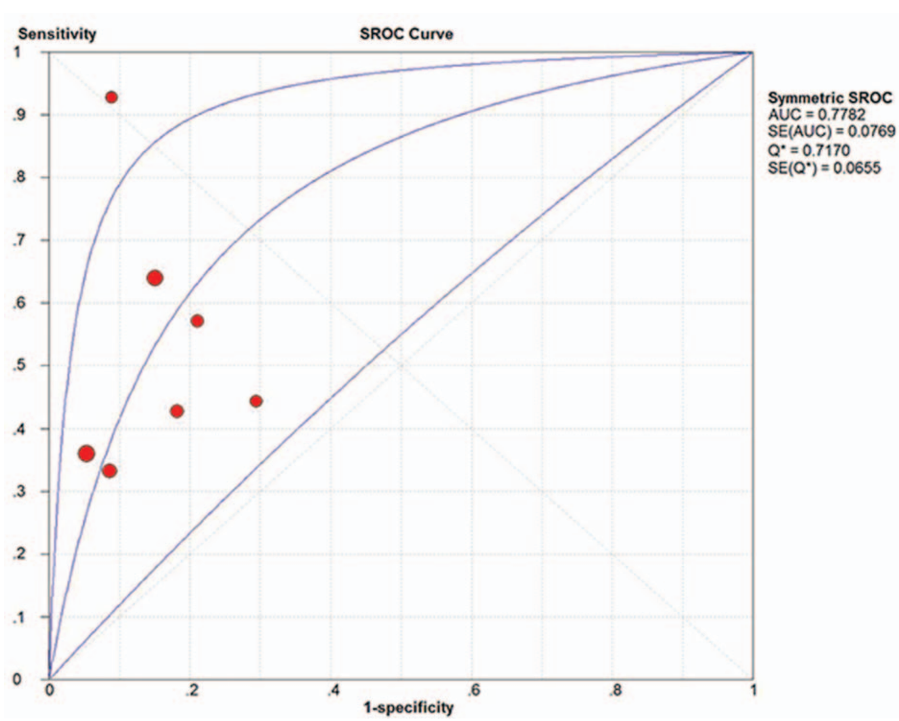

Figure 3. Summary receiver operating characteristic curve showing the performance of MRI for detecting lymph node metastases in prostate cancer patients on patient-based analysis. MRI = magnetic resonance imaging.

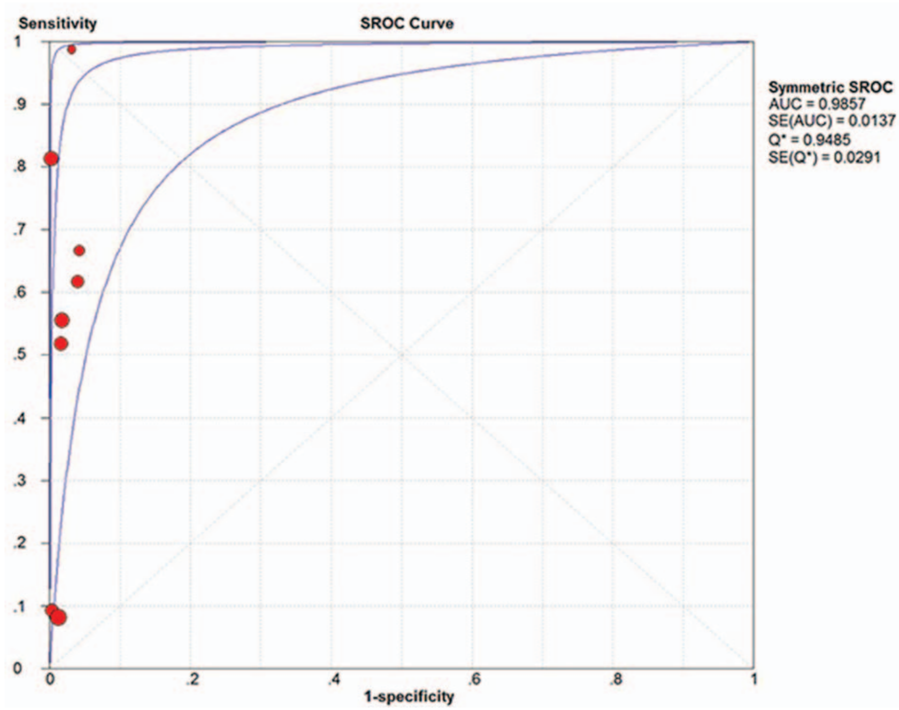

Figure 4. Summary receiver operating characteristic curve showing the performance of choline PET/CT for detecting lymph node metastases in prostate cancer patients on node–based data analysis. PET/CT = positron emission tomography/computed tomography.

is radical prostatectomy, which can greatly improve the survival rate. The literature[28] has pointed out that pelvic lymph node dissection for the treatment of PCa micrometastasis in patients with more clinical significance. Once PCa spreads to the lymph nodes, most cases may lose the opportunity of cure with radical prostatectomy, while in other cases it will be significantly diminished. Currently, 30% to 40% of patients relapse after therapy, and about half of these patients are due to metastasis that were overlooked at the primary staging (mainly caused by lymph node metastases).[29] In addition, direct surgical treatment

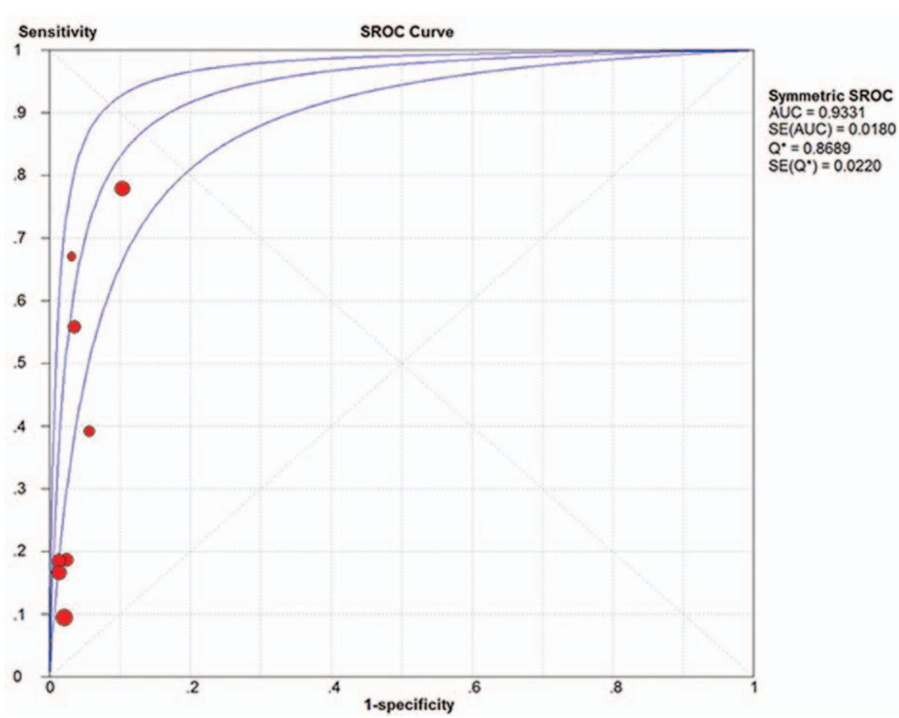

Figure 5. Summary receiver operating characteristic curve showing the performance of MRI for detecting lymph node metastases in prostate cancer patients on node-based data analysis. MRI = magnetic resonance imaging.

will inevitably bring patients suffering and financial burden, such as the early prediction of patients with lymph node metastasis, not only can reduce the burden on patients, while the treatment options and prognosis of great significance. However, the exact mechanism of PCa metastasis is not yet clear, and the diagnosis and treatment options are also controversial. As the presence of lymph node metastases in PCa patients is an important prognostic factor leading to a higher risk for progression, distant metastases, and death, the detection of lymph node is crucial for further treatment planning.[30,31]

At present, radical prostatectomy combined with pelvic lymph node dissection (LND) remain the most reliable and accurate way to diagnose PCa lymph node metastasis and stage., which could only detect lymph node metastases inside the surgical field.[32] However, lymph nodal involvement may be underestimated. And there is no conclusive evidence of the benefit of LND for nodal recurrence of PCa, particularly in terms of survival outcomes. Even extent of LND is reported that 13% of metastatic lymph nodes have been missed.[33] So there is still controversial about extent of LND. In most PCa patients, the initial seeding of metastatic deposits comes up in lymph nodes, as demonstrated by extended pelvic lymph nodes dissection in surgical.[34] Lymph nodal dissection performed by either open surgery or laparoscopy, is invasive, associated with morbidity and complication (ranging from 4% to 5%), and may failing to sample all potential lymph nodal.[35] Therefore, the decision of lymphadenectomy should be guided by the preoperative probability of LN metastases.[36] In addition, imaging can detect more LN metastases outside the surgical field.

Traditional morphological imaging technique MRI which is primarily dependent on morphological assessment based on the size, shape, and adjacent structure invasion of the lymph nodes has been widely used in the staging of PCa, with a lymph node short axis diameter <1 cm and is considered to be normal.[37] Only an oval node with a short axis diameter of 10 mm and a round lymph node with a short axis diameter of 8 mm generally accepted as the upper limit of normal. However, it is not sufficient to use size as a criterion to determine lymph node status in PCa patients, as it has been reported that up to 80% lymph node metastasis of newly diagnosed PCa patients occur in normal-sized lymph node (<8 mm).[38] Moreover, it is difficult for MRI to identify small lesions and distinguish between the benign findings and potential metastatic lesions.[32] Moreover, reactive hyperplasia may enlarge nonmetastatic lymph nodes.[39] However, PET/CT imaging could help to provide more reliable information.

Molecular imaging technique PET/CT, which combines the metabolic activity depicted by PET with the tissue anatomical structure by CT in a single diagnostic session using a single device, could overcome the limitations of MRI. In 2012, choline was approved by the US Food and Drug Administration as an imaging agent to be used to detect PCa during PET imaging. Choline kinase could be upregulated in the PCa cells of the primary cancer and its lymph node metastases. Therefore, radioactively labeled choline PET/CT imaging can differentiate PCa cells from neighboring noncancer tissue. Due to the low-spatial resolution of PET imaging (approximately 5 mm in clinical scanners), choline PET/CT was unable to detect subcentimeter node metastasis. It is known that choline is also accumulating in inflammatory diseases, animal models on inflammation, experimental bacterial infections.[40] Therefore, the diagnosis of choline PET/CT positive lymph nodes requires an important differential diagnosis from inflammatory diseases.[40] In addition to that choline PET/CT imaging may be limited for the differentiation of malignant and benign lesions which is particularly important in lymph nodes. Therefore, the diagnosis of choline PET/CT positive lymph nodes requires an important differential diagnosis from inflammatory diseases. In addition, due to ^{11}C-choline only has a short half-life of 20 minutes, its clinical use is not a widely available option. This deficiency stimulates the development of ^{18}F-choline, and its longer half-life (half-life of 110 minutes) allow for long-distance transportation and long-time storage. Nevertheless, ^{11}C-choline is less excreted into the urinary system compared to ^{18}F-choline, which could effectively reduce the radioactive background and increases the high uptake of tumor tissue.[41] Therefore, aware of the advantages and disadvantages of choline PET/CT for detecting lymph node metastasis of PCa patients is very important.

The published studies evaluating the lymph node stage show different and conflicting results.[10] In one of clinical studies, Hacker et al[42] reported a low sensitivity of 10% on a per patient-based analysis (TP in 1, FN in 9) in a study of 20 patients assessed with choline PET/CT. In their study, however, the largest lymph node metastasis not seen with choline PET/CT was 8 mm and the mean diameter of metastatic lymph node was 3.8 mm which is below the spatial resolution of PET/CT imaging. Conversely, de Jong et al[13] achieved promising results using choline PET/CT for detecting lymph node metastases in 67 PCa patients, with a sensitivity of 80% (95%CI 57%– 98%) and specificities of 96% (95% CI 84%–99%) on patient-based analysis. However, about 50% of patients with lymph node metastasis have high PSA values (>50 ng/mL), which may lead to selection bias. In more recent studies, Beheshti et al[14] and Schiavina et al[10] who used choline found in 130 and 57 patients, respectively, sensitivities of 45% (95% CI 29%–62%) and 60% (95% CI 32%–83%) and specificities of 96% (95% CI 89%–99%) and 98% (95%CI 87%–100%), respectively. There is no consensus on whether choline PET-CT should be applied to lymph node staging.

Our meta-analysis included 8 original research studies which directly compare the diagnostic performance and clinical utility of choline PET/CT and MRI. In addition, we found that choline PET/CT were more accurate than MRI for detecting lymph node metastases in patients with PCa. This study has shown that when considering patient-based analysis, there is no significant difference in sensitivity between PET/CT (0.59%[95%CI (0.50–0.67)] and MRI (0.52%[95%CI (0.44–0.61]), but choline PET/CT offers a better specificity of 92%(95%CI: 87%–96%) than MRI 87%(95%CI: 81%–92%). However, if we focus on the nodes-based analysis, the sensitivity of choline PET/CT to detect lymph node metastasis is suboptimal (51%, 95%CI: 46%–57%), although it is better than MRI (39%, 95%CI: 34%–44%). And there is no significant difference in specificity between PET and MRI. Since due to choline may also accumulate in inflammatory tissue, it is not specific for PCa as a metabolic tracer uptake of inflammatory nodes However, the results of this study show that the specificity of choline PET/CT imaging was higher than that of MRI. Meanwhile, the present results showed there was a rather low sensitivity with choline PET/CT or MRI suggesting that choline PET/CT or MRI in its present form is not ideal for lymph node staging of PCa.

Like all meta-analysis of diagnostic accuracy, our study also has been limited by the degree of heterogeneity, including radiologist or nuclear medicine physician experience, patient selection, methodological quality and approach to image interpretation. A further crucial limitation is the fact that there is no uniform acceptable gold standard, which is general weakness of various imaging modality for diagnostic efficiency in the diagnosing lymph node metastasis and most studies researching different tumors. As we all know, histological confirmation is the gold standard of lymph node metastases. However, due to the deep location of partially metastatic lymph nodes, it is technically and morally difficult to perform histopathological analysis for all histopathological changes, so the application of histopathological and clinical follow-up as a reference standard is unavoidable. In 8 of these included studies, 6 studies were using histopathology as reference standard, whereas histopathology and clinical follow-up were used in the other 2 studies. The negative findings under the reference standard of clinical follow-up were negative only during the follow-up, and the final findings may be TP, which may cause verification bias to our results. Due to this meta-analysis contains a limited number of studies, we did not conduct a subgroup analysis for the location of lymph node metastasis or the pathological type of prostate cance. In addition, we cannot rule out the presence of relevant original reports when completing the systematic review in a rapidly evolving field of research. At last, heterogeneity may also be due to some unreported or unmeasured research features, which are inherent in meta-analysis based on published data. We deal with the problem of heterogeneity in 3 ways: When selecting the studies use inclusive criteria to minimize diversity, performed stratified analysis base on the factors that may result in the heterogeneity,use the validated tool (QUADAS) to provide objective and strict evaluating of quality of included articles.

5. Conclusion

In this meta-analysis, choline PET/CT for detecting lymph node metastases from PCa showed higher specificity, LR+, LR−, DOR, AUC, and Q* than MRI on patient-based data analysis. On node-based data analysis, choline PET/CT showed higher sensitivity, LR +, LR−, DOR, AUC and Q* than MRI. Therefore, PET/CT had excellent accuracy for the diagnosis of lymph node metastases superior to MRI and had the potential to be broadly applied in clinical practice. However, choline PET/CT and MRI exhibited in the present study a rather low sensitivity with less than three-fifth of lymph node metastases being detected on patient-based and node-based data analysis. Due to the small sample size and large heterogeneity, current evidence does not justify the implementation of choline PET/CT for detecting lymph node metastases in PCa patients. Also MRI is still the most commonly used staging tool in daily clinical practice, despite its poor sensitivity and specificity to lymph node metastasis. However, with the increasing number of PET / CT centers, the use of ^{11}C or ^{18}F choline for staging of prostate cancer is increasing.

Author contributions

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