Diagnostic Evaluation of 18F-FDG PET/CT Imaging in Recurrent or Residual Urinary Bladder Cancer: A Meta-Analysis

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Abstract

**Purpose** To assess the diagnostic accuracy of fluorine-18 fluorodeoxyglucose positron emission tomography combined with the computed tomography (18F-FDG PET/CT) in the detection of recurrent or residual urinary bladder cancer with meta-analysis.

**Methods** We searched PubMed/MEDLINE, Embase, Web of Science, CBM, CNKI, VIP, and Wanfang databases through October 2019. Two reviewers independently screened the full articles. The imaging findings were confirmed by either histopathology or clinical follow-up. Sensitivity, specificity likelihood ratio and diagnostic odds ratio were pooled with 95% confidence intervals (CI). Overall test performance was summarized by a summary receiver operating characteristic (ROC) curve. The Meta-DiSc software (version 1.4) was used to perform the meta-analysis.

**Results** The meta-analysis included 7 studies. The pooled sensitivity and specificity of PET/CT for the detection of recurrent or residual urinary bladder cancer was 94.0% (95% CI: 91.0%–96.0%) and 92.0% (95% CI: 88.0%–95.0%), respectively. Positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio were 9.77 (95% CI: 4.91–19.41), 0.99 (95% CI: 0.06–0.13) and 95.09 (95% CI: 47.96–188.53), respectively. When residual urinary bladder cancer was excluded, sensitivity changed slightly.

**Conclusion** This meta-analysis suggested that the diagnostic accuracy of PET/CT was good in detecting recurrent or residual urinary bladder cancer.
Introduction

Bladder cancer is the most common urinary tract cancer with a high mortality rate in worldwide, in 2012 the estimated diagnosed new cases were about 430 000 \(^{(1)}\). Despite continuing advances in surgical and nonsurgical therapeutic strategies, the patients with urinary bladder cancer have higher risk of recurrence and residue. Cystoscopy is still the gold standard for the diagnosis of bladder cancer, but can still miss 10% of papillary tumors \(^{(2)}\). Contrast-enhanced computed tomography and MRI are the commonly used imaging techniques for bladder cancer diagnosis, but these methods are not very high with an accuracy rate ranged from 35% to 55% in CT and 62% to 85% in MRI \(^{(3,4)}\).

18F-FDG PET/CT has been reported as non-invasive imaging methods for many malignancies, but it’s using is limited due to the high urinary excretion activity of the bladder and ureters \(^{(5)}\). Recently, several studies have assessed the application value of 18F-FDG PET/CT in detection recurrence and residue of bladder carcinoma. However, the population of bladder cancer patients was small and results were inconclusive. The aim of our study was to explore the diagnostic accuracy of 18F-FDG PET/CT in the detection of recurrent or residual bladder cancer by a meta-analysis.

Methods

Literature search strategy

We performed a comprehensive search from the electronic literature databases of PubMed/MEDLINE, Embase, Web of Science, and Chinese databases (CBM, CNKI, VIP, and Wanfang database). The search was performed from the earliest available date of
indexing to October 2019. Our search strategy included terms of “PET, positron emission tomography”, “FDG, fluorodeoxyglucose” and “bladder cancer”. Two authors independently screened articles. We also scanned references of articles which were included in the study.

Data collection and analysis

All included studies based on the following criteria: (i) adult patients with primary bladder cancer; (ii) using 18F-FDG PET/CT for detecting the recurrence and residue of bladder lesions; (iii) definite histological or follow-up outcome; (iv) studies providing the number of true-positive, true-negative, false-positive, and false-negative.

The exclusion criteria were as follows: (i) the total number of true positives, false positives, true negatives, and false negatives was not provided; (ii) abstracts, reviews, editorials, comments and letters.

Data extraction and quality assessment

The following information: first author’s name, publication year, country of the study population, patients’ characteristics (number of patients, mean age, gender), study design (retrospective or perspective), doses of 18F-FDG and furosemide, reference test (histopathology or clinical follow-up was ascertained as the golden standard, all imaging findings were confirmed by either histopathology or clinical follow-up.), imaging time, sensitivity and specificity data were retrieved. Two reviewers independently reviewed articles and disagreements were resolved by consensus after re-evaluation of the references. Research quality was assessed using the standards of the QUADAS-2 tool (6).
which was developed as a validated tool for diagnostic studies. The QUADAS-2 consist of four domains: (1) patient selection, (2) index test, (3) reference standard and (4) flow and timing. Those indexes describe the quality of the included studies and heterogeneity. The egger test was not conducted as included studies were less than 10.

Statistical analysis

We reported data based on the guidelines of meta-analysis evaluating diagnostic tests. Sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR–) and diagnostic odds ratio (DOR) had been presented. It is commonly used to add 0.5 to all counts in the table automatically when zero values exist \(^7\). Pooled sensitivity and specificity also displayed with 95% confidence intervals. \(I^2\) index was used to evaluate heterogeneity between included studies. A summary receiving operator characteristics (ROC) curve and area under the curve (AUC) were used to testify the overall accuracy of 18F-FDG PET/CT based on selected studies. All meta-analyses were performed using the Meta-DiSc software (version 1.4) \(^8\).

Result

Literature Review

A total of 316 publications about FDG PET/CT for recurrent or residual urinary bladder cancer was eligible for inclusion. After reviewing the titles, abstracts and full texts, 305 studies had been removed in Fig. 1. Of the remaining 11 studies, 1 study was excluded by reviewing the full text because of unclear classification \(^9\), 2 studies were excluded since the test was conducted only in the patients who were confirmed recurrent
or residual urinary bladder cancer \(^{(10,11)}\). Besides 1 study \(^{(12)}\) was excluded from our meta-analysis because 2 studies were from the same team, one in English and one in Chinese. Although the sample quantities of the two articles were different, the final valid data were the same, and we finally chose the English article. Therefore, 7 studies \(^{(13-19)}\) finally met the inclusion criteria. The information of the included studies was listed in Table 1 and Table 2.

**Qualitative analysis (systematic review)**

Among the 7 included publications, 6 studies were published in English and 1 study in Chinese. Those included studies were conducted in five different counties. The sample size ranged from 22 to 287. All the studies were retrospective, included a valid reference test, and the imaging time was 1 hour after the FDG injection. Furosemide was used in 3 of the selected studies, and 5 studies used additional pelvic delayed imaging to better show bladder lesions. The graph of QUADAS-2 displays the evaluation of the risk of the bias and concerns regarding applicability of those selected study (Fig.2). In current study, no obviously bias was observed.

**Quantitative analysis (meta-analysis)**

603 patients included in the 7 studies had bladder lesions. Pooled sensitivity and specificity were calculated by a random effects model. The sensitivity was 0.94 (95 % CI, 0.91 to 0.96, Q=7.73, P=0.2588), and specificity was 0.92 (95 % CI, 0.88 to 0.95, Q=25.13, P=0.0003) (Fig. 3 and Fig. 4). The overall LR+, LR– and DOR were 9.77 (95% CI: 4.91–19.41), 0.09 (95% CI: 0.06–0.13) and 95.09 (95% CI: 47.96–188.53), with the
Q value of 12.20, 3.94 and 5.53 respectively (all P>0.05). The SROC curve represents a global test performance which is based on the combination of sensitivity and specificity. The Q* index is defined as the maximum joint sensitivity and specificity, where the probabilities are equal for sensitivity and specificity. Fig. 5 showed the SROC curves of 18F-FDG PET/CT for recurrent or residual urinary bladder cancer. The Q* index was 0.9197. The AUC was 0.9699, indicating that the overall accuracy was relatively high.

Subgroup analysis

When residual urinary bladder cancer was excluded, sensitivity changed slightly while there was no change in specificity. The pooled sensitivity of PET/CT for the detection of recurrent urinary bladder cancer was 93.0% (95% CI: 90.0–96.0%). Positive likelihood ratio was 10.66.

Discussion

Medical imaging technologies played a critical role in clinical oncology. Clinicians could locate where a tumor is with the help of molecular imaging that can visualize the expression and activity of specific molecules which are very important to the future of patients. Accurate assessment of the recurrence and/or residue of bladder lesions is critical for follow-up treatment of bladder cancer patients. Usually, CT and MRI are widely used in the disease surveillance after bladder preservation therapy. Residual or recurrent lesions are difficult to be identified morphologically due to the shape change of the bladder wall after treatment. PET/CT plays an important role in the diagnosis, staging
and therapy monitoring of malignant diseases (24), and can generally detect the activity of biological tumors (11). In urinary tumors, FDG-PET/CT has been used to accurately assess lymph nodes or distant metastases, but is rarely used to image recurrent or residual lesions (25-27), primarily due to the high concentration of FDG in the urine (28). In order to improve 18F-FDG PET/CT imaging, several strategies such as adequate hydration, bladder irrigation and forced diuresis with furosemide have been used to delay PET/CT imaging of bladder tumors (29,30).

We identified 7 studies comprising 603 patients and the pooled sensitivity and specificity of 18F-FDG PET/CT for the detection of recurrent or residual urinary bladder cancer was 94.0% and 92.0%, respectively. Among those studies, 5 of 7 studies used additional pelvic delayed imaging in order to better show bladder lesions (13-16,18). The results showed a relatively high sensitivity and specificity. The Q value (0.9197) which represents the highest common value of sensitivity and specificity and the AUC (0.9699) which is the area under ROC curve demonstrate that 18F-FDG PET/CT is accurate diagnostic methods for the detection of recurrent or residual urinary bladder cancer. Thus, 18F-FDG PET/CT has an accurate and effective diagnostic performance for recurrent or residual urinary bladder cancer.

Our meta-analysis still exist some limitations. All forms of meta-analyses can not avoid publication bias. For example, non-significant or negative studies are often rejected and conference abstracts, letters to journal studies were excluded in our meta-analysis. We rechecked all documents in the search stage, including conference papers, and find that
no conference abstracts, letters meet the inclusion criteria. Considering the methodological evaluation according to QUADAS-2, publication bias was not obviously in current analysis. Besides, language barrier was existed because the studies which we searched were published in English or Chinese only, so studies published in other languages would be omitted. Second, several studies had small sample size. Furthermore, the heterogeneity such as study design, imaging techniques and quality of the selected studies was existed.

**Conclusion**

Overall, we observed that 18 F-FDG PET/CT is an effective means for the detection of recurrent or residual urinary bladder cancer. A large randomized trial is needed to demonstrate the diagnostic capability of 18F-FDG PET/CT in detection of urinary bladder lesions.

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**Conflict of Interest**

All authors declare that they have no conflicts of interest.
References


Fig. 1 Flow chart showed detailed information for eligible studies selection.

Fig. 2 Methodological evaluation according to QUADAS-2 of the included studies
Fig. 3 Sensitivity for 18 F-FDG PET/CT in detection of recurrent or residual urinary bladder cancer.
Fig. 4 Specificity for 18 F-FDG PET/CT in detection of recurrent or residual urinary bladder cancer.

Fig. 5 SROC curves for 18F-FDG PET/CT for recurrent or residual urinary bladder cancer.