REVIEW

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

Minmin XUE, MM, Liping LIU, MB, Guanghui DU, MM, Zhigang FU, MM*

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.

Keywords: bladder cancer; FDG PET/CT; sensitivity; specificity; meta-analysis

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 highly diagnostic 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.

Department of Health Management Center, 983 Hospital of Joint Logistics Support Force, Tianjin, 300142, China.
*Correspondence: Health Management Center, 983 Hospital of Joint Logistics Support Force, 60 Huangwei Road, Hebei District, Tianjin, China.
Tel: (022)84683128, Fax: (022)84683128, Email: fuzhigang983@126.com.
Received August 2019 & Accepted December 2019

Table 1. Characteristics of the selected studies

Study	Year	Country	Patients, n	Sex (M/F)	Age (years)	Image time	Reference test	Design	Furosemide	FDG dose
S Harkirat (13)	2010	India	22	-	-	Dual phase: 1 h after FDG injection; 60-90 min after furosemide	PA or FU	R	0.5 mg/kg of furosemide	370 MBq (10 mCi)
Yang Z (14)	2012	China	35	28/7	Mean:56 35-96	1 h after FDG injection; additional pelvic images: unknown	PA or FU	R	-	7.4 MBq/kg
Yildirim-Poyraz N (15)	2013	Turkey	51	42/9	Mean:63.6 32-78	Dual phase: 1 h after FDG injection; 30-45 min after furosemide	PA or FU	R	0.5 mg/kg of furosemide	0.15 mCi/kg
Li H (16)	2014	China	84	-	-	Dual phase: 1 h after FDG injection; 2 h after furosemide	PA or FU	R	furosemide 40 mg	270-350 MBq
Kitajima K (17)	2016	Japan	83	66/17	Mean:69.7 36-88	1 h after FDG injection	PA, FU or RI	R	-	4.0 MBq/kg
Alongi P (18)	2016	Italy	41	36/5	Mean± SD 67 ± 10	Dual phase: 1 h and 90–120 min after FDG injection	PA or FU	R	-	3.7MBq/Kg
Zattoni F (19)	2017	Italy	287	223/64	Mean± SD 69 ± 10	1 h after FDG injection	PA or FU	R	-	3-3.8 MBq/Kg

R: retrospective; PA: pathology; FU: follow-up including physical examination, laboratory tests, and serial imaging, such as CT or MRI.

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

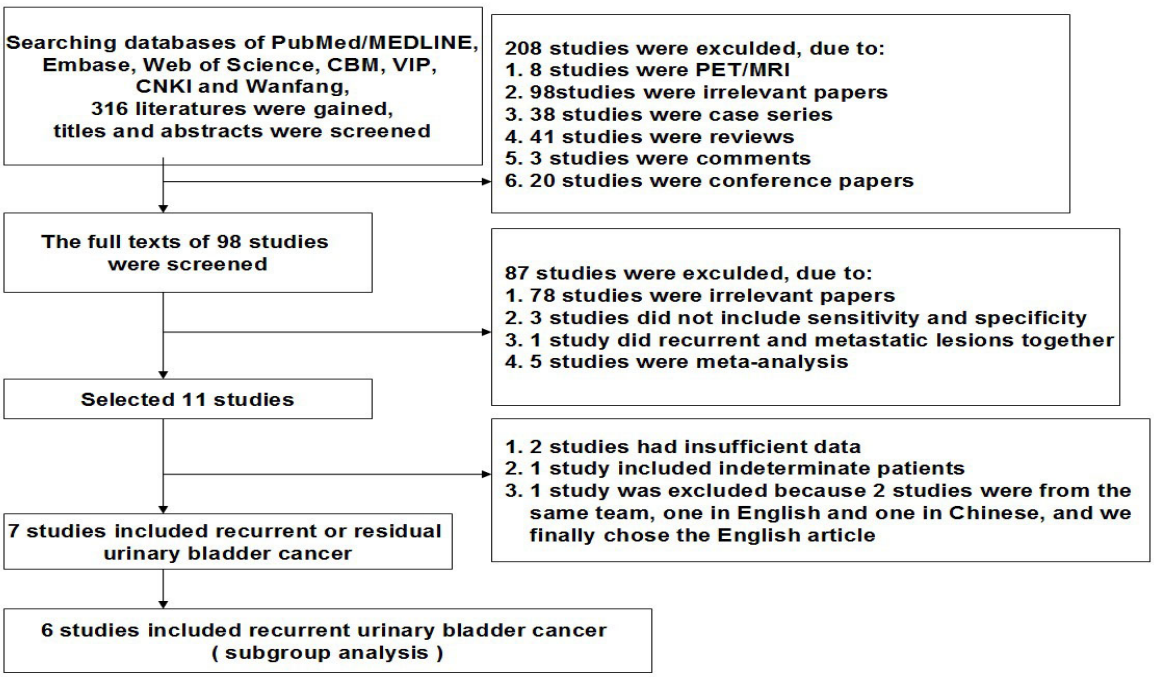

Figure 1. Flow chart showed detail information for eligible studies selection.

Table 2. Diagnostic accuracy data of 18F-FDG PET/CT imaging in recurrent or residual urinary bladder cancer

author	year	Recurrence or Residue				Recurrence			
		TP	FP	TN	FN	TP	FP	TN	FN
S Harkirat (13)	2010	13	0	7	2	13	0	7	2
Yang Z (14)	2012	11	3	20	1	11	3	20	1
Yildirim-Poyraz N (15)	2013	30	2	19	0				
Li H (16)	2014	22	3	57	2	22	3	57	2
Kitajima K (17)	2016	8	0	75	0	8	0	75	0
Alongi P (18)	2016	20	1	17	3	20	1	17	3
Zattoni F (19)	2017	189	11	38	11	189	11	38	11

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 consists 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. I2 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].

RESULTS

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 were removed (**Figure 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 (**Figure 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) (**Figures 3 and 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. **Figure**

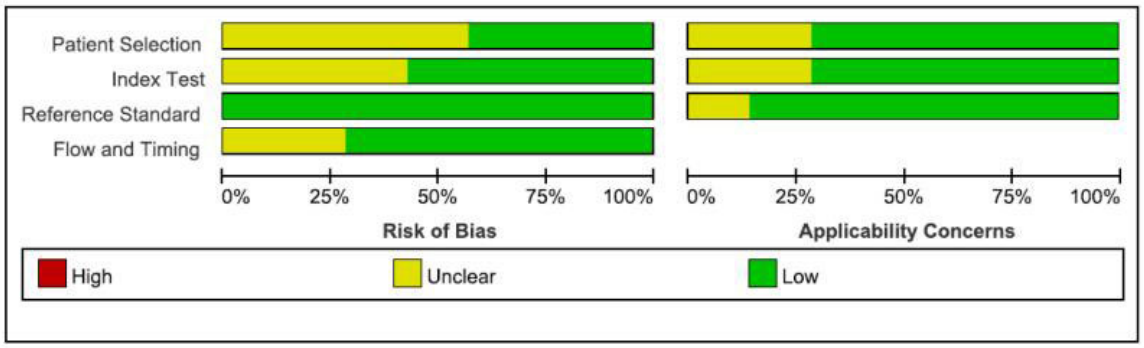

Figure 2. Methodological evaluation according to QUADAS-2 of the included studies.

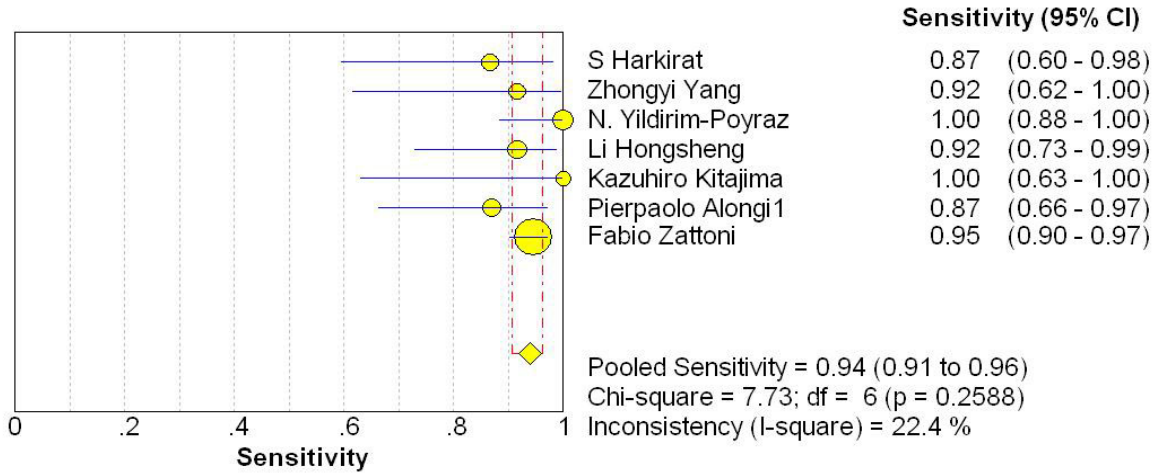

Figure 3. Sensitivity for 18 F-FDG PET/CT in detection of recurrent or residual urinary bladder cancer.

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[20,21]. 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[22]. Residual or recurrent lesions are difficult to be identified morphologically due to the shape change of the bladder wall after treatment[23]. 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

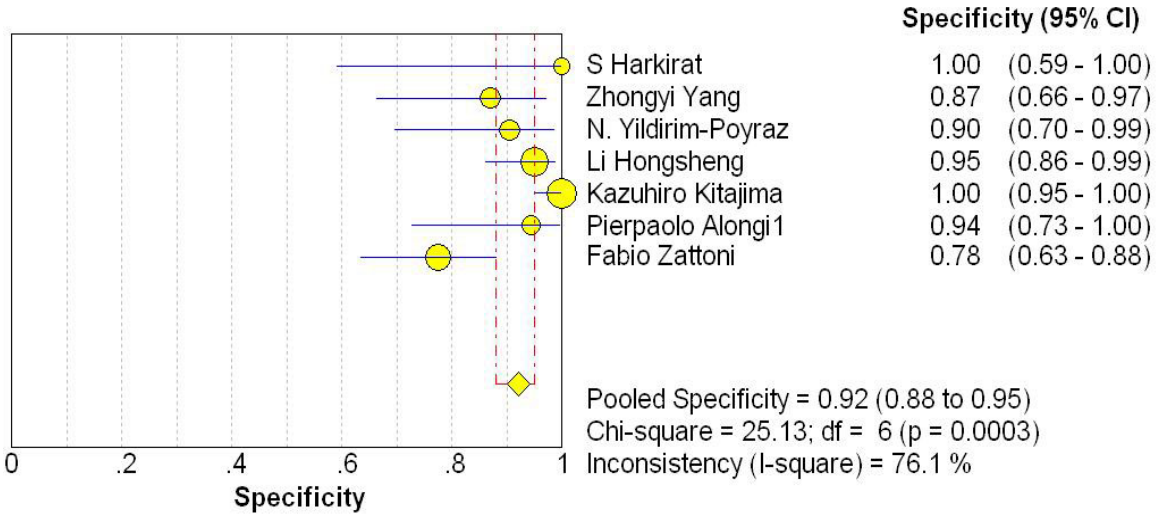

Figure 4. Specificity for 18 F-FDG PET/CT in detection of recurrent or residual urinary bladder cancer.

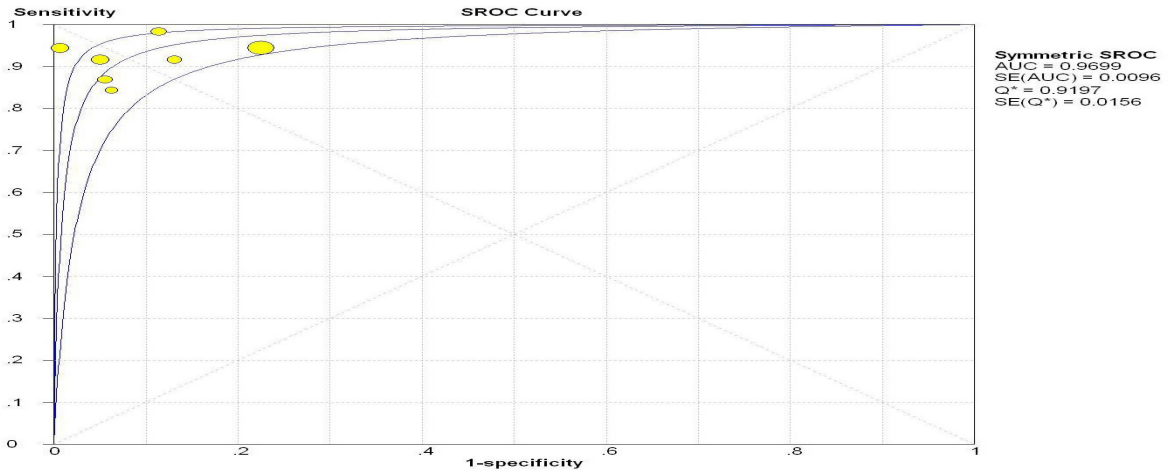

Figure 5. SROC curves for 18F-FDG PET/CT for recurrent or residual urinary bladder cancer.

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 has some limitations. All forms of meta-analyses cannot 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 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, heterogeneity in elements such as study design, imaging techniques and quality of the selected studies existed.

CONCLUSIONS

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.

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

REFERENCES

1. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. Eur Urol. 2017;71:96-108.
2. Loidl W, Schmidbauer J, Susani M, Marberger M. Flexible cystoscopy assisted by hexaminolevulinate induced fluorescence: a new approach for bladder cancer detection and surveillance? Eur Urol. 2005;47:323-6.
3. Paik ML, Scolieri MJ, Brown SL, Spirnak JP, Resnick MI. Limitations of computerized tomography in staging invasive bladder cancer before radical cystectomy. J Urol. 2000;163:1693-6.
4. Lawrentschuk N, Lee ST, Scott AM. Current role of PET, CT, MR for invasive bladder cancer. Curr Urol Rep. 2013;14:84-9.
5. Bouchelouche K, Oehr P. Positron emission tomography and positron emission tomography/computerized tomography of urological malignancies: an update review. J Urol. 2008;179:34-45.
6. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003;3:25.
7. 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.
8. Zamora J, Abraira 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.
9. Mertens LS, Fioole-Bruining A, Vegt E, Vogel WV, van Rhijn BW, Horenblas S. Detecting primary bladder cancer using delayed (18)F-2-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography imaging after forced diuresis. Indian J Nucl Med. 2012;27:145-50.
10. Kosuda S, Kison PV, Greenough R, Grossman

HB, Wahl RL. Preliminary assessment of fluorine-18 fluorodeoxyglucose positron emission tomography in patients with bladder cancer. Eur J Nucl Med. 1997;24:615-20.

11. Higashiyama A, Komori T, Juri H, Inada Y, Azuma H, Narumi Y. Detectability of residual invasive bladder cancer in delayed (18)F-FDG PET imaging with oral hydration using 500 mL of water and voiding-refilling. Ann Nucl Med. 2018;32:561-7.
12. Cheng J, Yang Z, Zhang Y, et al. Application of whole body 18F-FDG PET/CT plus additional delayed pelvic scan after oral hydration in the diagnosis of the bladder malignant lesions. CHINA ONCOLOGY. 2014;24:540-4.
13. Harkirat S, Anand S, Jacob M. Forced diuresis and dual-phase F-fluorodeoxyglucose-PET/CT scan for restaging of urinary bladder cancers. Indian J Radiol Imaging. 2010;20:13-9.
14. Yang Z, Cheng J, Pan L, et al. Is whole-body fluorine-18 fluorodeoxyglucose PET/CT plus additional pelvic images (oral hydration-voiding-refilling) useful for detecting recurrent bladder cancer? Ann Nucl Med. 2012;26:571-7.
15. Yildirim-Poyraz N, Ozdemir E, Uzun B, Turkolmez S. Dual phase 18F-fluorodeoxyglucose positron emission tomography/computed tomography with forced diuresis in diagnostic imaging evaluation of bladder cancer. Rev Esp Med Nucl Imagen Mol. 2013;32:214-21.
16. Li H, Wu H, Wang Q, Han Y, Wang Q. Value of the dual phase 18F-FDG PET/CT in the diagnosis of recurrent and metastatic bladder cancer after surgery. China Academic Journal. 2014;30:1450-3.
17. Kitajima K, Yamamoto S, Fukushima K, et al. FDG-PET/CT as a post-treatment restaging tool in urothelial carcinoma: Comparison with contrast-enhanced CT. Eur J Radiol. 2016;85:593-8.
18. Alongi P, Caobelli F, Gentile R, et al. Recurrent bladder carcinoma: clinical and prognostic role of 18 F-FDG PET/CT. Eur J Nucl Med Mol Imaging. 2017;44:224-33.
19. Zattoni F, Incerti E, Colicchia M, et al. Comparison between the diagnostic accuracies of 18F-fluorodeoxyglucose positron emission tomography/computed tomography and conventional imaging in recurrent urothelial carcinomas: a retrospective, multicenter study. Abdom Radiol (NY). 2018;43:2391-9.
20. Weissleder R. Molecular imaging in cancer. Science. 2006;312:1168-71.
21. Hoffman JM, Gambhir SS. Molecular imaging: the vision and opportunity for radiology in the future. Radiology. 2007;244:39-47.
22. Alfred Witjes J, Lebret T, Comperat EM, et al. Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Eur Urol. 2017;71:462-75.
23. Zhang J, Gerst S, Lefkowitz RA, Bach A. Imaging of bladder cancer. Radiol Clin North Am. 2007;45:183-205.
24. Lawrence J, Rohren E, Provenzale J. PET/CT today and tomorrow in veterinary cancer diagnosis and monitoring: fundamentals, early results and future perspectives. Vet Comp Oncol. 2010;8:163-87.
25. Apolo AB, Riches J, Schoder H, et al. Clinical value of fluorine-18 2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography in bladder cancer. J Clin Oncol. 2010;28:3973-8.
26. Chakraborty D, Mittal BR, Kashyap R, et al. Role of fluorodeoxyglucose positron emission tomography/computed tomography in diagnostic evaluation of carcinoma urinary bladder: comparison with computed tomography. World J Nucl Med. 2014;13:34-9.
27. Goodfellow H, Viney Z, Hughes P, et al. Role of fluorodeoxyglucose positron emission tomography (FDG PET)-computed tomography (CT) in the staging of bladder cancer. BJU Int. 2014;114:389-95.
28. Zouhair A, Ozsahin M, Schaffer M, et al. Positron Emission Tomography and Computer Tomography (PET/CT) in Prostate, Bladder, and Testicular Cancers. Curr Med Chem. 2010;17:2492-502.
29. Anjos DA, Etchebehere EC, Ramos CD, Santos AO, Albertotti C, Camargo EE. 18F-FDG PET/CT delayed images after diuretic for restaging invasive bladder cancer. J Nucl Med. 2007;48:764-70.
30. Koyama K, Okamura T, Kawabe J, et al. Evaluation of 18F-FDG PET with bladder irrigation in patients with uterine and ovarian tumors. J Nucl Med. 2003;44:353-8.