RESEARCH ARTICLE

Diagnostic Accuracy of 18F-FDG-PET in Patients with Testicular Cancer: a Meta-analysis

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Abstract

Objective: Fluorine-18-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) is a new technique for identifying different malignant tumors using different uptake values between tumor cells and normal tissues. Here we assessed the diagnostic accuracy of 18F-FDG-PET in patients with testicular cancer by pooling data of existing trials in a meta-analysis. Methods: PubMed/MEDLINE, Embase and Cochrane Central Trials databases were searched and studies published in English relating to the diagnostic value of FDG-PET for testicular cancer were collected. The summary receiver operating characteristic (SROC) curve was used to examine the FDG-PET accuracy. Results: A total of 16 studies which included 957 examinations in 807 patients (median age, 31.1 years) were analyzed. A meta-analysis was performed to combine the sensitivity and specificity and their 95% confidence intervals (CIs), from diagnostic odds ratio (DOR), positive likelihood ratios (PLR), negative likelihood ratio (NLR). SROC were derived to demonstrate the diagnostic accuracy of FDG-PET for testicular cancer. The pooled sensitivity and specificity were 0.75 (95% confidence interval (CI), 0.70-0.80) and 0.87 (95% CI, 0.84-0.89), respectively. The pooled DOR was 35.6 (95% CI, 12.9-98.3). The area under the curve (AUC) was 0.88. The pooled PLR and pooled NLR were 7.80 (95% CI, 3.73-16.3) and 0.31 (95% CI, 0.23-0.43), respectively. Conclusion: In patients with testicular cancer, 18F-FDG-PET demonstrated a high SROC area, and could be a potentially useful tool if combined with other imaging methods such as MRI and CT. Nevertheless, the literature focusing on the use of 18F-FDG-PET in this setting still remains limited.

Keywords: ¹⁸F-FDG-PET - testicular cancer - diagnosis - meta-analysis

Asian Pac J Cancer Prev, 15 (8), 3525-3531

Introduction

Testicular cancer is the most frequently diagnosed malignancy in the age group of 20 to 40 years (Devesa et al., 1995), which is traditionally subdivided into seminomatous and nonseminomatous tumors. The worldwide incidence ranges from 0.5 to 9.9 cases per 100, 000 men per year, with extensive regional differences. And the most important risk factor remains cryptorchism and there is a variable association with testicular microlithiasis (Becherer, 2011). Before the use of cisplatin, the cure rates were less than 10% (Ganjoo et al., 1999). Today, testicular cancer is highly curable, with 5-year survival rates over 95% (Lewis et al., 2006). More than 90% of patients are cured with surgery, radiotherapy, and chemotherapy alone or combination of them (Yetisyigit et al., 2014). This success depends on the accuracy of disease diagnosis and the application of optimum treatment. Because of the excellent cure rates in testicular cancer, new diagnostic methods are needed to strengthen the diagnostic value for early diagnosis and correct staging to ensure that the optimum treatment strategy is employed.

In order to correctly evaluate patients with testicular cancer, a variety of diagnostic imaging modalities have been used. Computer tomography (CT) and magnetic resonance imaging (MRI) are the common imaging modalities in testicular cancer with the role in initial staging of patients, in assessment of cancer response and detection of disease relapse. However, dependence on structural abnormal conditions to identify disease means CT and MRI have many limitations. It cannot detect disease in "normal-sized" lymph nodes or cannot detect whether there is active tumor in residual masses after chemotherapy (Nichols, 1998; Huddart, 2003). As well as chest X-ray and ultrasound of the abdomen, they also have the same limitation. Tumor maker is another diagnostic sign, however, it also has limitations, because there is no serum tumor marker in the seminomatous tumors, only nonseminomatous tumor has tumor marker (Becherer, 2011); furthermore, tumor makers always have unsatisfied sensitivity and specificity. So, it is being active to explore new diagnostic method, in particular functional imaging, such as [18F] -fluorodeoxyglucose positron emission tomography, has significant advantage over anatomically

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Jing-Yi Zhao et al

derived imaging.

Fluorine-18-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) has been successfully used to evaluate different types of malignant tumors (Saunders et al., 1999; Czernin, 2002; Halfpenny et al., 2002; Johns Putra et al., 2004; Rohren et al., 2004; Chen et al., 2011), like esophagus, thyroid, nasopharyngeal and lung carcinoma (Mutlu et al., 2013; Uzel et al., 2013). FDG-PET is also a valuable tool for assessment of treatment response, and also an indicator of prognosis (Uzel et al., 2013). FDG is absorbed into cells in a way similar to glucose, but it is not metabolized and it accumulates in metabolically active cells and tissues. FDG-PET could identify tumor cells and normal tissues by the different metabolism of glucose and uptake values of FDG rather than structure image which depend on size (Czernin, 2002; Huddart, 2003; Karapetis et al., 2003). Many studies confirm that FDG is prior taken up by both seminomatous tumors and nonseminomatous tumors, which have been quantified on the basis of standard uptake values (SUV) (Wilson et al., 1995). The uptake values in both residual masses containing necrotic and benign differentiated teratoma are lower than that in active tumor (Stephens et al., 1996). Furthermore, FDG-PET has more advantages compared to CT and tumor makers, especially in patients with a negative CT scan, PET may be able to identify the metastatic lesion (Tsatalpas et al., 2002). Alecander Becherer et al. have reported that FDG-PET is superior to CT in the prediction of viable tumor in seminoma residuals after chemotherapy, with a sensitivity/specificity of 80%/100%, while CT had only 70%/74% (Becherer et al., 2005). Thus, FDG-PET is a new diagnostic method of testicular cancer through functional imaging rather than structure imaging.

The accuracy of FDG-PET for diagnosis of testicular cancer has been assessed in a series of studies. However, a meta-analysis of published data in this field is lack. The purpose of this study is to meta-analyze published data on the diagnostic performance of FDG-PET in patients with testicular cancer and to assess the overall accuracy of the functional imaging method in this setting.

Materials and Methods

Search strategy and study selection

A comprehensive computer literature search of the PubMed/MEDLINE, Embase and Cochrane Central Trials databases was conducted to find relevant published articles on the diagnostic accuracy of FDG-PET in patients with testicular cancer. We used the following search terms: "testicular cancer" and "PET". The search was performed from inception to April 2013. No language restriction was exposed. References of the retrieved articles were also screened for additional studies.

Inclusion and exclusion criteria were defined before the literature search. Studies were selected if they met the following criteria: (1) FDG-PET performed in patient with testicular cancer; (2) using histopathology of surgical specimens, or a follow-up period of at least 3 months as reference standard; and (3) providing data available to construct a 2×2 contingency table for true-positive, falsepositive, false-negative, and true-negative determination. Here, the sufficient data include both direct and indirect data in the studies. Direct data are shown in the article and can be picked up easily. Indirect data should be calculated backwards from the four numbers.

Studies were excluded if they met the following criteria: (1) did not evaluate testicular cancer; (2) incomplete data available; (3) were duplicated or updated; (4) reviews, editorials, corresponding letters that did not report their own data; and (5) case reports.

Two independent reviewers (JY Zhao and XL Ma) reviewed the titles and abstracts of the retrieved articles, applying the selection criteria mentioned above. Articles were excluded if they were clearly ineligible. The same two researchers then independently reviewed the fulltext version of the remaining articles to determine their eligibility for inclusion. Disagreements were resolved in consultation with a third reviewer after face-to-face discussion.

Statistical methods

Study-level analysis: Based on the value of truepositive (TP), true-negative (TN), false positive (FP), false negative (FN), we calculated the pooled sensitivity and specificity, positive and negative likelihood ratios (LR) and diagnostic odds ratio (DOR). The calculated statistics above were used to examine the FDG-PET accuracy for the diagnosis of testicular cancer. All statistics were reported as point values with 95% confidence intervals (CIs). Sensitivity was defined as the TP rates and calculated as TP/ (TP+FN). Specificity was defined and calculated as TN/ (FP+TN). LR indicates how much use of a given test would raise or decrease the probability of having disease. In this study, the PLR was the measure of the likelihood that a positive staging result of an index test would occur in a patient with testicular cancer, while the NLR was the measure of the likelihood that a negative staging result would occur in a patient without testicular cancer. The diagnostic odds ratio (DOR) is a single overall indicator of diagnostic performance and expresses how much greater the odds of having the disease for the people with a positive test result than for the people with a negative test result. The DOR was calculated as (TP x TN) / (FP x FN). In addition, summary receiver operator characteristics (SROC) curves were constructed to examine the interaction between sensitivity and specificity. We use the area under the curve (AUC) to measure the overall performance of the diagnostic test (Moses et al., 1993). Statistical analyses were performed using Meta-Disc statistical software version 1.4 and Stata software version 11.1.

<u>Meta-analysis-model</u>: The between-study heterogeneity was evaluated by computing Higgins's I² and X² tests for heterogeneity using the generic inverse variance method of meta-analysis. A random effects model is used for statistical pooling of the data in the case of heterogeneity between the studies (P<0.1); a fixed effects model for statistical pooling of the data is used if there was no heterogeneity between the studies.

Quality of studies: We assessed the quality of the included studies in this meta-analysis using a checklist

Author, year	Country No.0	of patients	No.of	Age (year)	PET technique	Reference	QUADAS	TP	FP	EN	Z
		exa	amination	2			score				
M.de Wit, 2008	Germany	72	72	28	18F-FDG 388 MBq 60 min uptake	histopathologic	14	21	1	11	39
M.Bachner, 2012	Europe, Israel Canada	125	127	NA	NA	histopathologic, follow-up data	10	14	19	٢	87
M.de Santis, 2004	Austria, Germany	51	56	NA	18F-FDG 370 MBq 45 min uptake	histopathologic, follow-up data	10	8	0	0	46
K.Oechsle, 2008	Germany	121	121	30	18F-FDG 200-400 MBq 45 min uptake	histopathologic	11	47	33	20	21
P. Tsatalpas, 2002	Germany	23	96	NA	18F-FDG 100-390 MBq 50-90 min uptake	histopathologic, follow-up data	10	22	8	З	63
U. Cremerius, 1999	Germany	50	50	31	18F-FDG 159-283 MBq 30-60 min uptake	histopathologic, follow-up data	11	13	0	0	33
C.Bokemeyer, 2002	Germany	23	23	31	18F-FDG 250-500 MBq 45-60 min uptake	follow-up data	10	14	0	0	Г
U. Cremerius, 1998	Germany	33	54	30	18F-FDG 120-309 MBq 40-80 min uptake	histopathologic, follow-up data	10	16	с	8	27
SF Hain, 2000	England	55	70	30	NA	histopathologic, follow-up data	10	36	0	8	24
P. Albers, 1999	Germany	37	37	NA	18F-FDG 185-370 MBq 45 min uptake	histopathologic, follow-up data	13	Г	0	З	27
A. Becherer, 2004	Austria, Germany	48	74	39	18F-FDG 370 MBq 45 min uptake	histopathologic, follow-up data	13	12	0	З	59
U. Lassen, 2003	Denmark	46	46	30	NA	follow-up data	13	٢	0	З	36
S. Hinz, 2008	Germany	20	20	42.5	NA	histopathologic	10	б	6	0	×
J.R.Spermon, 2002	Netherland	50	58	30	18F-FDG 200-220 MBq 60 min uptake	histopathologic, follow-up data	13	14	0	4	38
J. Siekiera, 2012	Poland	37	37	NA	NA	histopathologic	12	9	0	0	29
Z. Akbulut, 2011	Turkey	16	16	29	18F-FDG 350-400 MBq 60 min uptake	histopathologic	10	5	-	8	0
NA, indicates not avail	able, TP, true-positive; F	FP, false-pos	sitive; FN	, false-negativ	e; TN, true-positive						



Figure 1. Flow Chart of Selection Process for Eligible Studies

based on the quality assessment for the studies of 50.0 diagnostic accuracy (QUADAS) tool (Whiting et al., 2003). It has 14 items to evaluate the quality of studies. Each item may be scored "yes" if reported; "no" if not25.0 reported; or "unclear" if there is no adequate information in the article. The quality assessment was done by JY Zhao and XL Ma independently. Disagreements were resolved in consultation with a third reviewer after face-to-face 0 discussion.

<u>Publication bias</u>: Publication bias was assessed using Begg's funnel plots and test (p > 0.05 was considered that there was no potential publication bias) (Deeks et al., 2005). The Begg's funnel plots and test were performed by Stata 11.0.

Results

Study Selection and Characteristics of studies in our analysis

The comprehensive computer literature search from the PubMed/MEDLINE, Embase, and Cochrane Central Trials databases revealed 179 articles, 37 potentially relevant studies were restricted for evaluation. Ultimately, 21 studies were excluded for undesirable article types (n=21), not written in English (n=6), and insufficient data (n=4), letter (n=2), case report (n=1), and review (n=8). Thus, 16 studies were included in our final dataset for the meta-analysis (Cremerius et al., 1998; Albers et al., 1999; Cremerius et al., 1999; Hain et al., 2000; Bokemeyer et al., 2002; Spermon et al., 2002; Tsatalpas et al., 2002; Lassen et al., 2003; De Santis et al., 2004; Becherer et al., 2005; de Wit et al., 2008; Hinz et al., 2008; Oechsle et al., 2008; Akbulut et al., 2011; Bachner et al., 2012; Siekiera et al., 2012). The flowchart of study selection was shown in Figure 1.

Table 1 summarized the main characteristics of the included studies. A total of 893 examinations in 807 patients (median age, 31.1 years) were evaluated. Histopathologic findings or follow-up data were used as the reference standard for the final result of PET for testicular tumor in nine studies. Five studies included patients who were only referred to histopathologic findings, and two studies referred to follow-up data (Table 1). Detailed information about the QUADAS

Asian Pacific Journal of Cancer Prevention, Vol 15, 2014 3527

Jing-Yi Zhao et al

Table 2. Quality Assessment

Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality
															score
M.de Wit et al 2008	Yes	14													
M.Bachner et al 2012	Yes	Yes	Yes	Yes	Yes	No	Yes	?	Yes	?	?	Yes	Yes	Yes	10
M.de Santis et al 2004	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	?	?	Yes	Yes	Yes	10
K.Oechsle et al 2008	Yes	No	?	?	Yes	Yes	Yes	11							
P. Tsatalpas et al 2002	Yes	No	Yes	?	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	10
U. Cremerius et al 1999	Yes	No	Yes	Yes	Yes	No	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes	11
C. Bokemeyer et al 2002	No	Yes	Yes	Yes	Yes	No	Yes	Yes	?	Yes	Yes	Yes	Yes	?	10
U. Cremerius et al 1998	Yes	No	Yes	?	?	No	Yes	10							
SF Hain et al 2000	Yes	No	Yes	Yes	Yes	Yes	No	?	?	Yes	Yes	Yes	Yes	Yes	10
P Albers et al 1999	Yes	No	Yes	13											
A Becherer et al 2004	Yes	No	Yes	Yes	Yes	Yes	Yes	13							
U Lassen et al 2003	Yes	?	Yes	Yes	Yes	Yes	Yes	Yes	13						
S Hinz et al 2008	No	?	Yes	Yes	Yes	Yes	Yes	?	?	Yes	Yes	Yes	Yes	Yes	10
J.R. Spermon et al 2002	Yes	No	Yes	13											
J. Siekiera et al 2012	Yes	?	?	Yes	Yes	Yes	Yes	Yes	12						
Z. Akbulut et al 2011	Yes	?	Yes	Yes	Yes	Yes	Yes	Yes	?	?	?	Yes	Yes	Yes	10

Methodological Quality was assessed using Quality assessment of diagnostic accuracy studies criteria. Quality item 1: Was the spectrum of patients representative of the patients who will receive the test in practice? Quality item 2: Were selection criteria clearly described? Quality item 3: Is the reference standard likely to correctly classify the target condition? Quality item 4: Is the time period between reference standard and index test short enough to be sure that the target condition did not change between the two test? Quality item 5: Did the whole sample, or a random selection of the sample, receive verification using a reference standard of diagnosis? Quality item 6: Did patients receive the same reference standard regardless of the index test result? Quality item 7: Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard?) Quality item 8: Was the execution of the index test described in sufficient detail to premin replication of the test? Quality item 9: Was the execution of the results of the regerence standard? Quality item 11: Were the index test results interpreted without knowledge of the results of the index test? Quality item 12: Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? Quality item 13: Were uninterpretable/intermediate test results reported? Quality item 14: Were withdrawals from the study explained?



Figure 2. A. Forest Plot of Sensitivity and Specificity of PET for Detection of Testicular Cancer B. Likelihood Ratios of PET for Detection of Testicular Cancer

questionnaire of the selected studies is shown in Table 2. The overall quality of the studies was good, with most items rating as "yes" rating for nearly all items.

Accuracy of PET for the diagnosis of testicular tumor

The meta-analysis was based on the extracted number of TP, TN, FP, and FN for the diagnosis of testicular cancer to assess the accuracy of FDG-PET in the included studies. The pooled sensitivity and specificity of FDG-PET was calculated using a random effects model. The pooled sensitivity and specificity of the PET measurement for the testicular tumor were 0.75 (95% CI, 0.70-0.80) and 0.87 (95% CI, 0.84-0.89), respectively (Figure 2A). The pooled PLR and pooled NLR were 7.80 (95% CI, 3.73-16.32) and 0.31 (95% CI, 0.23-0.43), respectively (Figure 2B). The pooled DOR was 35.57 (95% CI, 12.87-98.29, Figure 3), and the SROC was 0.88 (Figure 4). There were statistically significant heterogeneity in SPE ($X^2 P < 0.001$, I² =89.8%), PLR ($X^2 P < 0.001$, I² =89.7%) and DOR ($X^2 P = 0.001$, I² =78.5%), respectively. However, according to the meta-regression analysis, the accuracy of PET measurement was not affected by the covariates.

Assessment of publication bias

We used Begg's test and funnel plot to examine publication bias. Fortunately, there is no significant



Figure 3. DOR of PET for Detection of Testicular Cancer



Figure 4. The Summary Receiver Operating Characteristic (SROC) Curve and Q* index of Diagnostic Performance of PET in Evaluation of Testicular Cancer

publication bias in our analysis in results of meta-analysis of 16 studies for DOR (P = 0.857).

Discussion

To our knowledge, this meta-analysis is the first to evaluate the diagnostic performance of FDG-PET in patients with testicular cancer. We know now testicular cancer most frequently diagnosis in young men. Due to excellent cure rates in testicular cancer, new diagnostic methods are needed to correct diagnosis which is particularly important to choose a most appropriate therapeutic schedule. Several studies have reported the usefulness of FDG-PET in the diagnosis of testicular cancer (Czernin, 2002; Huddart, 2003). However, one of the major problems with these studies is that many have limitations, for their analyzing only relatively small numbers of patient. To derive more strong evaluates of diagnostic performance of FDG-PET we pooled published studies using meta-analysis.

In this meta-analysis, we evaluated the accuracy of FDG-PET, a non-invasive technique, using functional imaging rather than structure imaging for diagnosis testicular tumor. The results of our meta-analysis demonstrate that FDG-PET had a high diagnostic accuracy for accessing testicular cancer with a summary AUROC

of 0.88. According to this result, FDG-PET can be used in clinical practice as a good tool for the diagnosis of testicular cancer (Hanley and McNeil, 1982). The selection of a most appropriate treatment for testicular cancer is on the basis of early diagnosis and correct staging of the disease. Although biopsy is the gold standard for detection and characterization of testicular cancer, it is an invasive method and not fit for monitoring patients in clinical practice. In this respect, FDG-PET is promising and worthy to translate into clinical practice because it is a noninvasive and reliable method for the detection of testicular tumor. In addition, FDG-PET could be contributed to cancer staging by identifying lymphonodus that most likely to be malignant. The ease of practical and application, non-invasive character of FDG-PET make it increasingly popular among radiologist. In addition, FDG-PET demonstrated a good specificity, being a potentially useful tool if combined with other imaging methods.

However, this approach still has several limitations. Residual masses in the pelvis cause certain diagnostic problems due to adjacent urine activity. FGD-PET imaging is based on FDG uptake values; the uptake value in active tumor is higher than that in normal tissues. Excretion though urinary system and gather in bladder of FDG result in primary radiologist unable to distinguish the vicinal tumor with high uptake values. Sufficient hydration before FDG injection and emptying the bladder before the examination could overcome the problem. A second scan of the suspicious region after showing a wash-out bladder can also differentiate the tumor and urinary activity. Moreover, attenuation correction combined with iterative reconstruction algorithms help to differentiate small structures from bladder activity (Becherer et al., 2005).

Residual masses are larger than 3 cm in patients after chemotherapy is considered to be a problem for falsepositive results (Lewis et al., 2006). And another possible reason for false-positive is nonspecific inflammatory processes after chemotherapy (Kollmannsberger et al., 2002; Tsatalpas et al., 2002; Albers et al., 2004; Johns Putra et al., 2004). In this regard, it might be of principal importance that we should do the examination before chemotherapy or have an interval of at least 4 weeks after chemotherapy (De Santis et al., 2004; Becherer et al., 2005). Moreover, other imaging methods, such as CT, MRI, combined with FDG-PET can help to avoid the false-positive findings. And on the other hand, close cooperation between the physicians and those who explain the PET scan is very important to avoid these false-positive findings.

FDG-PET had an unsatisfactory sensitivity (0.75) and just a useful value of negative likelihood ratio (0.31). These values suggest that negative results of FDG-PET could not be used alone as a justification (McGee, 2002). False-negative and the unsatisfactory sensitivity may be given in following conditions. Micro-tumor and micro-metastases have lower uptake values which might be masked by the higher uptake of the primary tumor, which can infect the false-negative results (Hoekstra et al., 1993; Cremerius et al., 1998; Hofer et al., 2001; Spermon et al., 2002; Antoch et al., 2004). In addition, timing of the PET scan is important, for patients examined within 10-14 days

Jing-Yi Zhao et al

of chemotherapy may result in false-negative (Cremerius et al., 1998, Hain, 2005). In order to avoid these falsenegative results, a close cooperation between physicians and examiners are important. FDG-PET combined with other imaging methods can also help to overcome the problem. Moreover, another possible reason for falsenegative would be considered. Testicular cancer is divided into two major groups: seminoma and nonseminomatous germ cell cancer. The latter group consists of not only embryonal carcinoma, teratoma, yolk sac tumors, but other rare tumor types. FDG-PET scans cannot distinguish fibrosis from differentiated teratoma as both are low uptake values (Stephens et al., 1996; Sanchez et al., 2002; Dalal et al., 2006; Lewis et al., 2006; Becherer, 2011). In this connection, an enormous number of researches are required to make a new better criterion to identify vital teratoma and nonvital tissues.

Publication bias is a major concern in all forms of pooled analyses, as studies reporting significant results are more likely to be published than those reporting non-significant results. Indeed, it is not unusual for early small-sized studies to report a positive relationship that subsequent larger studies fail to repeat. Fortunately, in this meta-analysis, no significant publication bias was found by the Begg's test and funnel plot. The meta-regression did not show any relationship between the characteristics of studies and the diagnostic odds ratio.

Some limitations of this study should also be taken into consideration. First, many studies were excluded from the analysis, resulting in a small number of studies in the final meta-analysis. Second, the pooled results of the meta-analysis had high statistical heterogeneity. The heterogeneity has multiple sources, including differences in the reference test, difference in the study designs, differences in the subject populations, differences in cutoff values and differences in diagnostic modes (initial diagnosis or evaluation of residual masses after therapy). These could influence the stiffness value and lead to an overestimation of the true diagnostic performance.

In conclusion, 18F-FDG-PET is an accurate noninvasive and useful diagnostic tool for the patients with testicular cancer. FDG-PET is able to differentiate between nonvital and vital lesions in patients with testicular cancer. A negative PET eliminates viability in large lesions and contributes to avoid unnecessary surgery. On the other hand, a positive PET is a predictor of a viable tumor with the relapse risk. FDG-PET demonstrated a good specificity, being potentially useful tools if combined with other imaging methods such as MRI, CT. In addition, FDG-PET can provide uptake values, which can used as a prognostic factor in many tumors, and this is a new research hotspot. So, we also consider using it for predicting the prognosis depended on the difference of uptake values in tumor. In addition, planning of radiation therapy might become another application and research field for FDG-PET in the future.

Acknowledgements

The authors declare that they have no conflict of interest.

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DOI:http://dx.doi.org/10.7314/APJCP.2014.15.8.3525 Diagnostic Accuracy of 18F-FDG-PET in Patients with Testicular Cancer: A Meta-analysis

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