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ORIGINAL ARTICLE

Relationship between the expression of PD-1/PD-L1 and ^{18}F-FDG uptake in bladder cancer

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Abstract

Purpose Immunotherapy aimed at inhibiting the PD-1/PD-L1 immune checkpoint has been approved and used successfully for the treatment of bladder cancer. The identification of markers predictive of response to immune checkpoint inhibitors is critical to advancing the success of this therapy. ^{18}F-FDG PET/CT is a molecular imaging technique that can provide phenotypic information on malignant tumours. It is currently unknown whether there is a relationship between ^{18}F-FDG uptake and expression of PD-1/PD-L1 in bladder cancer. In this study, we investigated whether PD-1/PD-L1 expression is associated with ^{18}F-FDG uptake in bladder cancer, and whether ^{18}F-FDG PET/CT imaging can be used to predict the PD-1/PD-L1 status of bladder cancer.

Methods A retrospective analysis was performed in 63 patients with bladder cancer who had undergone ^{18}F-FDG PET/CT before surgical resection. Maximum standardized uptake values (SUVmax) were determined.

Results SUVmax was significantly higher in PD-1-positive patients than in PD-1-negative patients (33.0 ± 13.9 and 19.6 ± 14.2, respectively; $P = 0.032$), and in PD-L1-positive patients than in PD-L1-negative patients (29.1 ± 15.6 and 15.8 ± 11.4, respectively; $P < 0.0001$). In a multivariate analysis SUVmax was significantly associated with both PD-1 expression and PD-L1 expression ($P = 0.021$ and $P = 0.003$, respectively). Using a SUVmax cut-off value of 22.7, PD-1 status and PD-L1 status could be predicted with accuracies of 71.4% and 77.8%, respectively.

Conclusion Higher ^{18}F-FDG uptake by bladder cancer is associated with elevated PD-1/PD-L1 expression. ^{18}F-FDG PET/CT may be useful for predicting the PD-1/PD-L1 status of bladder cancer and for determining the optimal therapeutic strategy.

Keywords Bladder cancer · PD-1 · PD-L1 · PET/CT · SUVmax

Introduction

Bladder cancer is one of the most common malignant tumours and causes approximately 123,100 deaths globally each year [1]. Although in the majority of patients the disease is not invasive at diagnosis, in approximately 30% of patients the disease will progress to muscle-invasive bladder carcinoma, which carries a worse prognosis and elevated risk of distant metastasis [2, 3]. The treatment for bladder cancer depends largely on the stage of the disease. Despite great advances in treatment for bladder cancer that have led to improved survival, the treatment regimens for metastatic bladder cancer remained relatively unchanged over the decades until the discovery of immune checkpoint therapies that target programmed cell death protein (PD-1) and programmed death ligand 1 (PD-L1) [4–6]. However, the immune checkpoint agents approved for the treatment of metastatic bladder cancer have relatively low objective response rates that are correlated with the levels of expression of PD-1 or PD-L1 [7, 8]. Most patients with bladder cancer do not benefit from immune checkpoint therapies; it is therefore important to identify clinical characteristics that are predictive of PD-1 or PD-L1 expression status. To date, however, there are no validated

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biomarkers for the a priori selection of patients who may benefit from immunotherapy.

^{18}F-FDG PET/CT is a molecular imaging technique that is widely used for the diagnosis, treatment response monitoring, surveillance and prognostication in a variety of cancer types [9–12]. We have previously demonstrated that PET/CT imaging has the potential to predict certain molecular phenotypes of cancer, including FBP1 expression in hepatocellular carcinoma, lactate dehydrogenase A expression in lung adenocarcinoma, and HER2 status in gastric cancer [13–15]. However, the relationships between ^{18}F-FDG uptake and the expression of PD-1 and PD-L1 in bladder cancer, and the possible underlying mechanisms, are not clear.

In the present study, we investigated whether the expression of PD-1 or PD-L1 is associated with ^{18}F-FDG uptake, and whether ^{18}F-FDG PET/CT imaging can be used to predict the expression of PD-1 or PD-L1 in bladder cancer. To our knowledge, this is the first study to present evidence of the potential of ^{18}F-FDG PET/CT imaging to indicate PD-1 or PD-L1 status in bladder cancer, and to suggest that ^{18}F-FDG PET/CT may play a key role in informing optimal treatment strategies in patients with bladder cancer by predicting response to anti-PD-1 and anti-PD-L1 therapies.

Materials and methods

Study population

The study group comprised 63 patients with bladder cancer (51 men and 12 women; age range 43–85 years), all of whom had undergone ^{18}F-FDG PET/CT imaging followed by tumour resection at the Ren Ji Hospital (affiliated with Shanghai Jiaotong University) between January 2015 and February 2018. Patients were eligible for inclusion if they met the following criteria: treatment with transurethral resection of bladder tumour or radical cystectomy; adjuvant therapy not administered before ^{18}F-FDG PET/CT imaging; diagnosis of bladder cancer confirmed by histopathological examination of surgical specimens; availability of complete case records, including data on age, sex, tumour size, T stage and histological subtype; and availability of tissue specimens for immunohistochemical staining. Exclusion criteria were as follows: history of adjuvant therapy before ^{18}F-FDG PET/CT imaging, insufficient pathological size for immunohistochemical analysis, and incomplete clinical and pathological data. All 63 patients met these criteria and informed consent was waived for the study, which was approved by the Institutional Review Board of Ren Ji Hospital and was in accordance with the principles of the 2013 revision of the Declaration of Helsinki.

^{18}F-FDG PET/CT imaging

Blood glucose levels were measured and found to be less than 140 mg/dL at the time of ^{18}F-FDG administration. All patients received an intravenous injection of ^{18}F-FDG at a dose of 3.7 MBq/kg after fasting for at least 6 h and resting for 1 h. The mean uptake time was 50 ± 6 min. ^{18}F-FDG PET/CT scanning from groin to skull base (early PET/CT imaging) was performed using a whole-body scanner (Biograph mCT; Siemens, Erlangen, Germany). Delayed PET/CTimaging was performed 120 min after early PET/CT imaging. Patients received 20 mg of furosemide intravenously and an extra oral intake of at least 500 mL water. Patients were asked to void frequently until the time of delayed imaging when they were asked not to void to allow urine to accumulate in the bladder. Delayed imaging covered a range of two bed positions centred on the bladder. PET images were attenuation-corrected and anatomically correlated with low-dose CT images.

For quantitative analysis, irregular regions of interest were placed over the most intense areas of ^{18}F-FDG uptake on delayed PET/CT images. Maximum standardized uptake values (SUVmax) were calculated as: [maximum pixel activity value within the decay-corrected region of interest (megabecquerels/millilitre)]/[injected dose (megabecquerels)/kilogram body weight]. The PET/CT images were evaluated by two experienced nuclear medicine physicians.

Immunohistochemical analysis

Paraffin-embedded bladder cancer specimens were sectioned at 4 mm thickness using a microtome and stained for immunohistochemical analysis as previously described [14]. Sections from tumours that matched those analysed with ^{18}F-FDG PET were also analysed immunohistochemically. Positivity for PD-1 and PD-L1 was evaluated using light microscopy by two independent pathologists, who were blinded to patient clinical information. The percentage of immune-reactive areas covered by PD-1 (indicating tumour-infiltrating lymphocytes) and PD-L1 was quantified. Tumours with >1% staining for PD-L1 were considered PD-L1-positive [16]. Staining of tumour-infiltrating lymphocytes for PD-1 was recorded as “absent”, “moderate” or “marked”. Tumours were considered PD-1-positive if staining was recorded “marked” [17].

Statistical analysis

Data are presented as means ± standard deviations (SD). The significance of differences between groups was determined using the *t* test, chi-squared test or Fisher’s exact test, where applicable. A P value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 13.0 (SPSS Inc., Chicago, IL, USA).

Table 1 Patient and tumour characteristics (n = 63)

Characteristic	Value
Sex, *n*	
Male	51
Female	12
Age (years)	
Mean ± SD	66 ± 9.6
Range	43-85
Surgery, *n*	
Radical cystectomy	38
Transurethral resection of bladder tumour	25
Histological subtype, *n*	
Pure urothelial cancer	59
Subtype of urothelial cancer	4
SUVmax	
Mean ± SD	20.9 ± 14.6
Range	3-63.8
PD-1 expression, *n*	
Negative	57
Positive	6
PD-L1 expression, *n*	
Negative	39
Positive	24

Results

Patient population

Patient and tumour characteristics are listed in Table 1. Of the 63 patients, 38 were treated with radical cystectomy and 25 underwent transurethral resection of the bladder tumour. Of the 63 patients, 59 had urothelial cancer, while four had different histological variants of urothelial cancer, including squamous cell carcinoma (three patients) and signet ring cell carcinoma (one patient). The SUVmax from delayed PET/CT imaging for the primary tumours ranged from 3 to 63.8, with an average of 20.9. Of the 63 primary tumours, 6 (9.5%) were PD-1-positive and 24 (38.1%) were PD-L1-positive. Representative histological sections showing PD-1 and PD-L1 expression are shown in Fig. 1.

Correlation between SUVmax and expression of PD-1 and PD-L1

Expression of PD-1 and PD-L1 in the 63 tumours was evaluated by immunohistochemical analysis There was a positive association between SUVmax from delayed PET/CT imaging and expression of both PD-1 (Fig. 2a) and PD-L1 (Fig. 2b). SUVmax was significantly higher in PD-1-positive tumours than in PD-1-negative tumours (33.0 ± 13.9 and 19.6 ± 14.2,

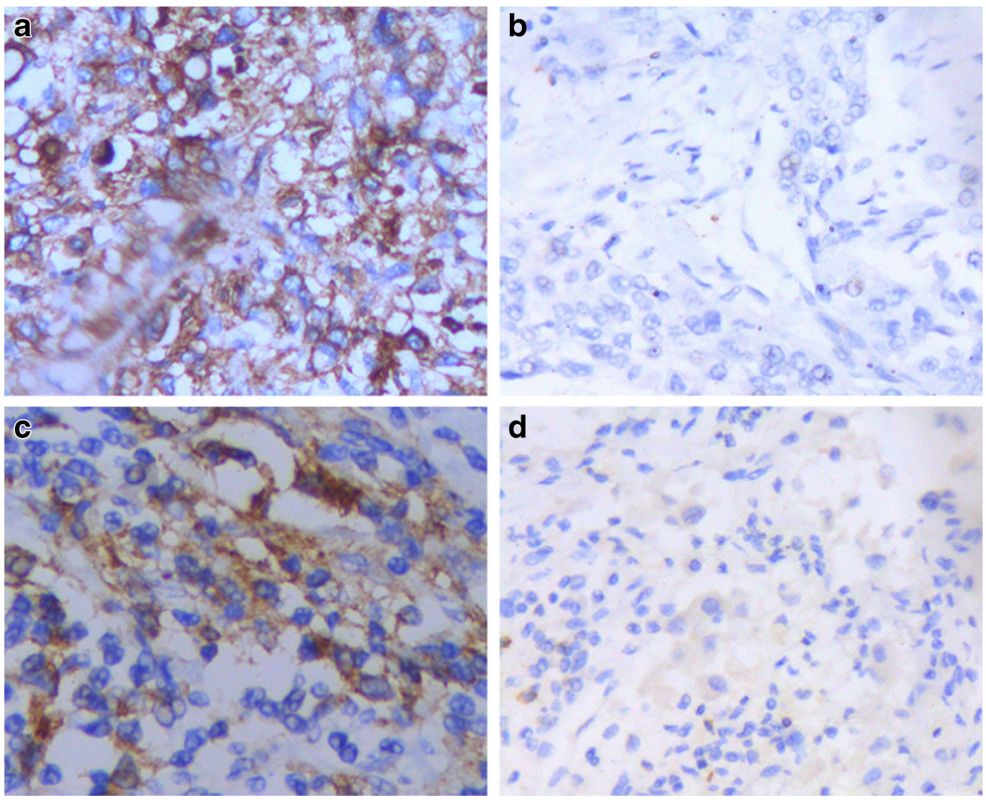

Fig. 1 Representative sections of bladder cancer tissue showing of PD-L1 and PD-1 expression (×200). **a** Positive PD-L1 expression in tumour. **b** Negative PD-L1 expression in tumour. **c** Positive PD-1 expression in tumour-infiltrating lymphocytes. **d** Negative PD-1 expression in tumour-infiltrating lymphocytes

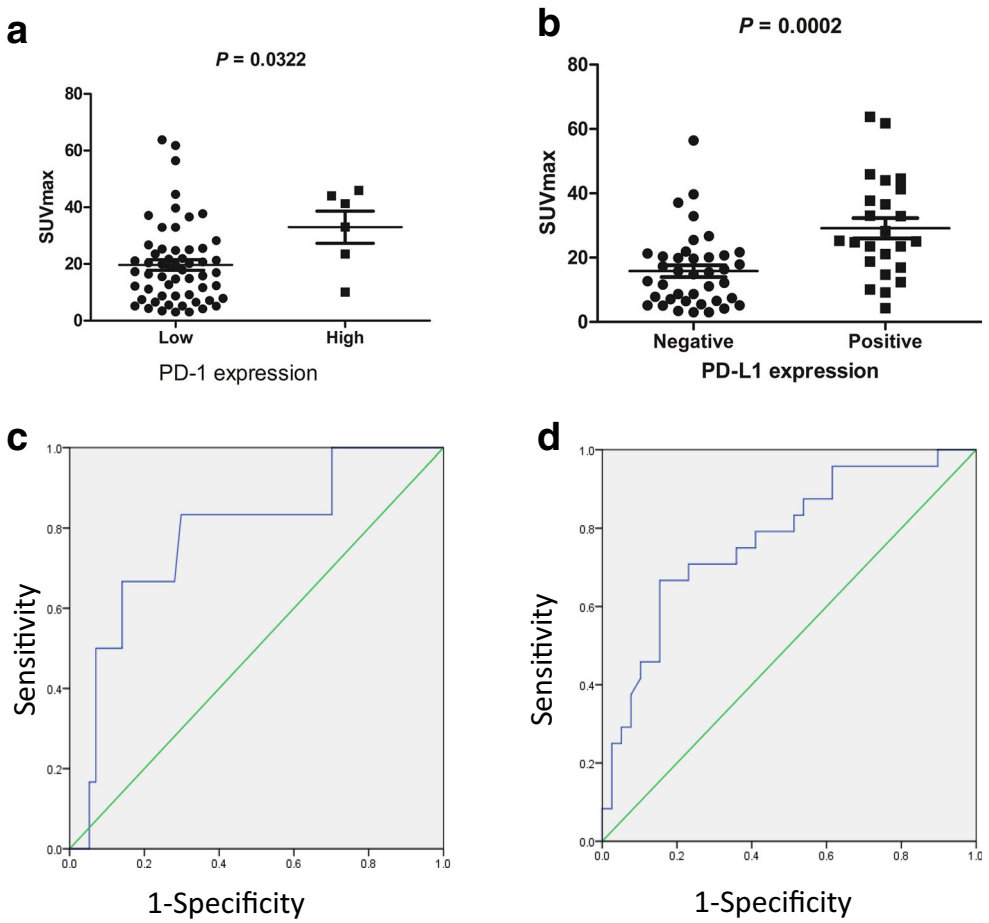

Fig. 2 Relationships between ^{18}F-FDG SUVmax from delayed PET/CT imaging and expression of PD-1 and PD-L1 in 63 bladder tumours. **a** Correlation between ^{18}F-FDG SUVmax and PD-1 expression. SUVmax is significantly higher in PD-1-positive tumours than in PD-1-negative tumours (33.0 ± 13.9 vs. 19.6 ± 14.2, respectively; $P = 0.032$). **b** Correlation between ^{18}F-FDG SUVmax and PD-L1 expression. SUVmax is significantly higher in PD-L1-positive tumours than in PD-L1-negative tumours (29.1 ± 15.6 vs. 15.8 ± 11.4, respectively; $P < 0.0001$). **c** Receiver operating characteristic curve analysis of the ability of SUVmax to predict PD-1 expression. Using a cut-off value of 22.7, the sensitivity and specificity of SUVmax in predicting PD-1 expression were 83.3% and 70.2%, respectively. The area under the receiver operating characteristic curve is 0.779 (95% confidence interval 0.59–0.97; $P = 0.025$). **d** Receiver operating characteristic curve analysis of the ability of SUVmax to predict PD-L1 expression. Using a cut-off value of 22.7, the sensitivity and specificity of SUVmax in predicting PD-L1 expression were 66.7% and 84.6%, respectively. The area under the receiver operating characteristic curve is 0.773 (95% confidence interval 0.65–0.89; $P < 0.0001$)

respectively; $P = 0.032$), and in PD-L1-positive tumours than in PD-L1-negative tumours (29.1 ± 15.6 and 15.8 ± 11.4, respectively; $P < 0.0001$).

Next the optimal SUVmax threshold for predicting PD-1 and PD-L1 expression was determined. Receiver operating characteristic (ROC) curve analysis showed that the highest accuracy (71.4%) for predicting PD-1 expression was obtained with a SUVmax cut-off value of 22.7 that resulted in an area under the curve of 0.779 ± 0.1. The sensitivity and specificity for predicting PD-1 expression were 83.3% (5/6) and 70.2% (40/57), respectively (Fig. 2c). Similarly, ROC curve analysis showed that the highest accuracy (77.8%) for predicting PD-L1 expression was obtained with a SUVmax cut-off value of 22.7 that resulted in an area under the curve of 0.773 ± 0.062. The sensitivity and specificity for predicting PD-L1 expression were 66.7% (16/24) and 84.6% (33/39), respectively (Fig. 2d). These results suggest that ^{18}F-FDG PET/CT may be useful in the assessment of the expression of PD-1 and PD-L1 in bladder cancer.

Correlations between patient characteristics and expression of PD-1 and PD-L1

Patients were categorized into two groups according to the results of the immunohistochemical analysis of PD-1 and PD-L1 expression. Associations between the clinical characteristics of the 38 patients treated with radical cystectomy and expression of PD-1 and PD-L1 were evaluated by univariate analysis (Table 2). Because no distant

Table 2 Univariate analysis of the relationship between PD-1/PD-L1 expression and clinicopathological characteristics of 38 patients with bladder cancer

Variable	No. of patients	PD-1 expression		*P* value	PD-L1 expression		*P* value
		Positive	Negative		Positive	Negative	
Sex							
Male	32	5	27	0.672	12	20	0.184
Female	6	1	5		4	2	
Age (years)							
<60	12	1	11	0.369	4	8	0.351
≥60	26	5	21		12	14	
Tumour size (cm), mean ± SD		4.9 ± 2.96	3.24 ± 3.15	0.242	3.47 ± 3.4	3.56 ± 2.7	0.934
T stage							
≤1	13	0	13	0.019	2	11	0.039
2	7	0	7		3	4	
3/4	18	6	12		11	7	
Lymph node metastasis							
Negative	34	5	29	0.513	15	19	0.433
Positive	4	1	3		1	3	
Histological subtype of urothelial cancer							
Pure urothelial cancer	35	6	29	0.588	14	21	0.369
Subtype of urothelial cancer	3	0	3		2	1	
SUVmax, mean ± SD		32.97 ± 13.94	17.14 ± 12.2	0.007	28.49 ± 15.22	13.19 ± 7.59	0.0413

metastasis occurred, the relationship between expression of PD-1/PD-L1 and M stage was not evaluated. No significant differences in sex, age, tumour size, lymph node metastasis or urothelial cancer histological subtype were found between the PD-1-positive and PD-1-negative groups. However, the groups differed significantly in terms of SUVmax from delayed PET/CT imaging and T stage (Table 2). In a multivariate analysis SUVmax from delayed PET/CT imaging and T stage were significantly correlated with PD-1 and PD-L1 expression in the 38 patients with bladder cancer (Table 3).

Based on these parameters, the patients were categorized into groups based on the optimal SUVmax cut-off and T stage to assess the probability of being PD-1-positive or PD-L1-positive: a low-probability group (T1/2 and SUVmax ≤22.7), a moderate-probability group (T1/2 and SUVmax >22.7, or T3/4 and SUVmax ≤22.7), and a high-probability group (T3/4 and SUVmax >22.7). The probabilities of being PD-1-positive in these groups were 0%, 9.1% and 50.0%, respectively ($P = 0.002$; Table 4), and the probabilities of being PD-L1-positive were 17.6%, 36.4% and 90.0%, respectively ($P = 0.001$; Table 4).

Table 3 Multivariate analysis of PD-1 and PD-L1 expression in 38 patients with bladder cancer

	Factor	Odds ratio	95% confidence interval	*P* value
PD-1	T stage	3.7	1.08–12.6	0.045
	SUVmax	15	1.5–148	0.021
PD-L1	T stage	4.7	1.18–18.8	0.028
	SUVmax	16.9	2.6–109	0.003

Discussion

Immune checkpoint agents have been approved for the treatment of metastatic bladder cancer [4–6]. Expression of PD-1 and PD-L1 within a tumour predicts response to treatment with anti-PD-1/PD-L1 antibodies [6], and evaluating PD-1/PD-L1 expression is commonplace in the clinical management of patients with bladder cancer. PET/CT imaging is widely used in the diagnosis and staging of malignant tumours. Although previous studies have demonstrated a correlation between PD-1/PD-L1 expression and SUVmax in lung cancer [18–20], the relationship between PD-1/ PD-L1 expression and SUVmax in bladder cancer, and possible underlying mechanisms, are not clear. In this study, we found that ^{18}F-FDG SUVmax was significantly higher in PD-1/PD-L1-positive bladder cancers than in PD-1/PD-L1-negative bladder cancers. To our knowledge, this is the first study to analyse the association between ^{18}F-FDG uptake and the expression of PD-1/PD-L1 in bladder cancer.

Table 4 Rates of positive PD-1 and PD-L1 expression among 38 patients with bladder cancer with low, moderate and high probabilities of PD-1/PD-L1 expression, as indicated by SUVmax and T stage

Probability	No. of patients	PD-1 expression (%)		*P* value	PD-L1 expression (%)		*P* value
		Negative	Positive		Negative	Positive	
Low	17	100	0	0.002	82.4	17.6	0.001
Moderate	11	90.9	9.1		63.6	36.4	
High	10	50	50		10	90	

Immunotherapy targeting PD-1/PD-L1 has been used successfully to treat a variety of malignant tumours, including bladder cancer [21–24]. However, the clinical characteristics associated with benefit from immunotherapy remain largely unknown, and identifying patients who are likely to receive meaningful benefit from PD-1/PD-L1 blockade while excluding those who are likely to be unresponsive to the treatment remains an unresolved challenge. The expression of PD-1/PD-L1, as assessed by immunohistochemistry, has been tested as a predictive biomarker of response to checkpoint inhibitors in bladder cancer. However, the procedure requires invasive biopsy, and alternative noninvasive strategies, such as PET/CT, that can predict PD-1/PD-L1 expression and could inform treatment strategies involving anti-PD-1/PD-L1 antibodies in patients with bladder cancer would be of great value.

We found a significant correlation between ^{18}F-FDG SUVmax and expression of PD-1/PD-L1 in bladder cancer. The receiver-operating-characteristic curves and the area under the SUVmax curve indicated that ^{18}F-FDG uptake could potentially be used to infer PD-1/PD-L1 expression. In the multivariate analysis both the SUVmax of the primary tumour and T stage were significant predictors of PD-1/PD-L1 expression in patients with bladder cancer. Although ^{18}F-FDG PET/CT may be a useful surrogate for PD-1/PD-L1 protein expression in patients with bladder cancer, the mechanism of association between ^{18}F-FDG uptake and PD-1/PD-L1 expression remains unclear. HIF1α is known to play an important role in regulating aerobic glycolysis, and can increase ^{18}F-FDG uptake [25, 26]. Moreover, hypoxia-inducible factor 1α (HIF-1α) binds directly to the hypoxia-responsive element (HRE) in the proximal promoter of PD-L1 and upregulates PD-L1 expression [27]. These findings suggest that the positive correlation between ^{18}F-FDG uptake and PD-1/PD-L1 expression may reflect activation of the HIF-1α pathway. In addition, Chang et al. found that antibody-mediated PD-L1 blockade or PD-L1 silencing inhibits the AKT/mTOR signalling pathway, resulting in reduced translation of mRNAs encoding glycolytic enzymes in cancer cells, and suggesting that PD-L1 is a modulator of glycolysis (^{18}F-FDG uptake) in cancer cells [28]. The regulatory capacities of PD-L1 over the mTOR pathway have also been demonstrated in another study [29].

We categorized patients with bladder cancer into groups based on their probability of being PD-1-positive or PD-L1-positive, as indicated by SUVmax and T stage: high probability, moderate probability, and low probability. PD-1 was expressed in 50.0% of the patients in the high-probability group, but in none of the patients in the low–probability group. Similarly, PD-L1 was expressed in 90.0% of the patients in the high-probability group, but in only 17.6% of the patients in the low-probability group. These findings suggest that anti-PD-1/PD-L1 therapies may not be suitable for patients with a low probability of being PD-1/PD-L1-positive. Novel immunotherapeutic approaches are being developed to inhibit the PD-1/PD-L1 axis. Noninvasive methods, such as molecular imaging, that can be used to infer PD-1/PD-L1 status, are therefore of great clinical relevance, and have the potential to predict the effect of anti-PD-1/PD-L1 immunotherapy in bladder cancer.

Our study was in part limited by its retrospective design and small sample size. Although PET/CT may have moderate diagnostic performance, in the clinical setting it is not possible to establish a SUV cut-off value, and PET/CT may not be able to replace conventional methods for determining PD-1/PD-L1 status. Nonetheless, our results may advance the development of noninvasive strategies for predicting PD-1/PD-L1 expression in patients with bladder cancer. Advances in PET radiotracers may increase the sensitivity and specificity of this technique, and enable full molecular assessment of bladder cancer by noninvasive means.

Conclusion

Bladder cancers with positive expression of PD-1/PD-L1 show higher ^{18}F-FDG uptake. Metabolic imaging has the potential to become a useful complement in the assessment of the molecular profiles of bladder cancer, and may be useful for predicting the response of bladder cancer to anti-PD-1/PD-L1 antibody therapies. Additional large, prospective clinical studies are required to confirm our results, and to determine whether metabolic imaging could be used not only to infer the PD-1/PD-L1 status of patients with bladder cancer, but also to assist in making the clinical decision as to whether to use an anti-PD-1/PD-L1 antibody therapy.

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were approved by the Institutional Review Board of Shanghai Jiao Tong University-affiliated Ren Ji Hospital and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This article does not describe any studies with animals performed by any of the authors.

Informed consent Informed consent was waived for the study.

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