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Case Report

Successful Treatment of Metastatic Urothelial Carcinoma after Accurate Diagnosis by Immunohistochemistry

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Urothelial carcinoma usually presents with hematuria, but cases of multiple lymphadenopathy with elevated S-pancreas-1 antigen (SPan-1) levels have not been reported. A 62-year-old Japanese man with lymphadenopathies was diagnosed with an adenocarcinoma of unknown origin and transferred to our hospital for further diagnosis. Serum carbohydrate antigen 19-9 and SPan-1 levels were extremely elevated. Uroplakin III immunostaining was positive in the inguinal lymph node, and cystoscopy revealed the presence of invasive urothelial carcinoma. Treatment with cisplatin and gemcitabine promoted a complete metabolic response for > 4 years. The detection of uroplakin III and serum SPan-1 might help diagnose urothelial carcinoma.

Key words: urothelial carcinoma, uroplakin III, s-pancreas-1 antigen, carbohydrate antigen 19-9, chemotherapy

Individuals with urothelial carcinoma usually present with hematuria and bladder irritation symptoms [1]. However, multiple lymphadenopathy with elevated levels of serum S-pancreas-1 antigen (SPan-1) is not regarded as an initial presentation of this disease. Here we describe the case of a patient with multiple metastatic invasive urothelial carcinoma with elevated serum SPan-1 and carbohydrate antigen 19-9 (CA19-9) levels that was successfully treated with chemotherapy. Uroplakin III, a specific membrane protein of urothelial umbrella cells, was a useful histological marker to detect the origin of carcinoma metastases in this case.

Case Presentation

A 62-year-old Japanese man presented with multiple swollen lymph nodes and leg edema. Computed tomography (CT) showed the presence of multiple lymphadenopathies of the inguinal, para-aortic, cervical, and mediastinal lymph nodes (Fig. 1). Although he was diagnosed by his previous physician with a metastatic adenocarcinoma based on the pathological features of an inguinal lymph node biopsy, there was no evidence indicating the site of the primary tumor. He was referred to our hospital for further examination.

A blood examination showed a normal complete blood cell count, elevated levels of D-dimer and tumor markers including carcinoembryonic antigen (CEA), CA19-9 and SPan-1, and normal urinary test results (Table 1). The inguinal lymph node biopsy results were reviewed in our hospital; they revealed atypical epithelial cells with an invasive micropapillary pattern, which indicated a carcinoma metastasis. There were no malig-

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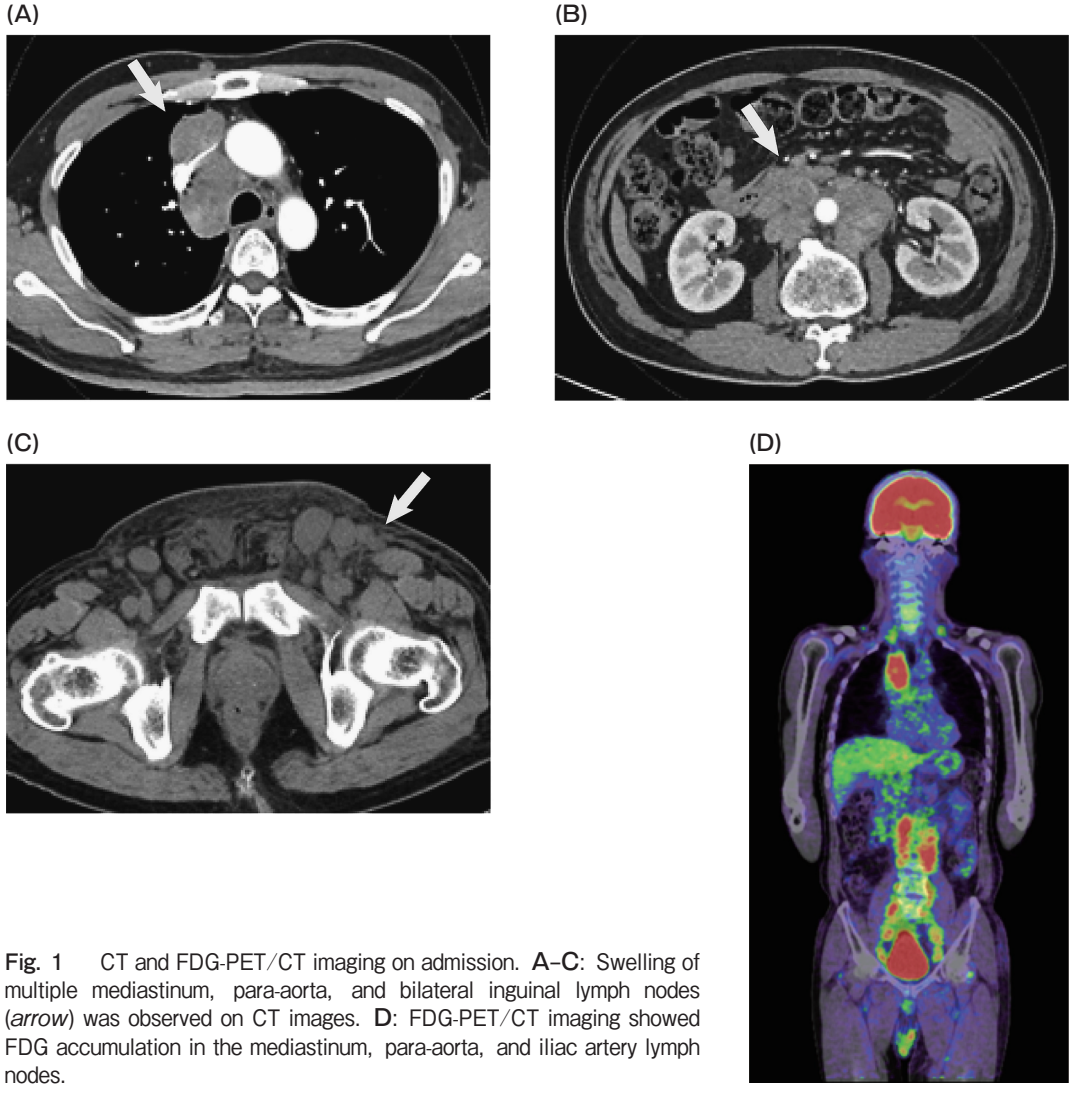

Fig. 1 CT and FDG-PET/CT imaging on admission. **A–C**: Swelling of multiple mediastinum, para-aorta, and bilateral inguinal lymph nodes (*arrow*) was observed on CT images. **D**: FDG-PET/CT imaging showed FDG accumulation in the mediastinum, para-aorta, and iliac artery lymph nodes.

nant primary lesions in the lung, gastrointestinal tract, or pancreas. He was transferred to our hospital with a diagnosis of adenocarcinoma of unknown origin with cancer-associated disseminated intravascular coagulation (DIC) and pulmonary embolism.

Fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) imaging showed multiple FDG accumulations in the cervical, supraclavicular, mediastinal, para-aortic, and inguinal lymph nodes. Further histological examination of the lymph nodes was performed. Immunohistochemical staining results of lymph node tumor cells were positive for cytokeratin (CK) 7, negative for CK20, negative for thyroid transcription factor-1 (TTF-1), negative for prostate-specific antigen, positive for S-100P, and positive with membranous staining pattern for uroplakin III (Fig. 2). We then considered the possibility of urothelial cell carcinoma. The urine cytology result was class V, and cystoscopy showed a pedunculated papillary tumor in the prostatic urethra. The histological examination revealed that the urethral tumor was an invasive urothelial carcinoma with histological features identical to those of the tumor of the inguinal lymph node (Fig. 3).

A diagnosis of invasive urothelial carcinoma of the prostatic urethra (cT1N2M1 cStage IV) was made, and the patient underwent chemotherapy with cisplatin (70 mg/m^2) and gemcitabine (1,000 mg/m^2). The treatment was feasible and after 6 cycles of treatment, the lymph node metastases shrank and the tumor marker levels were reduced. We added four treatment cycles (at

Table 1 Laboratory data on admission

Complete blood count		
WBC	5,600	/μL
Ne	55	%
Ly	35	%
Mo	6.8	%
Eo	2.8	%
Ba	0.8	%
RBC	395	x10⁴/μL
Hb	13	g/dL
Hematocrit	37	%
Plt	28.2	x10⁴/μL

Coagulation		
PT	19	sec
APTT	35	sec
PT-INR	1.8	
FDP	24.7	μg/mL
D-dimer	15	μg/mL

Urinalysis	
pH	5.5
Protein	–
Glucose	–
Occult blood	–
Sediment	negative

Biochemistry		
AST	27	U/L
ALT	30	U/L
T-Bil	0.3	mg/dL
ALP	293	U/L
γ-GTP	40	U/L
LDH	263	U/L
Na	139	mEq/L
K	4.4	mEq/L
Cl	108	mEq/L
Ca	8.7	mg/dL
BUN	11	mg/dL
Cre	0.7	mg/dL
CRP	0.4	mg/dL

Tumor marker		
β-HCG	1.1	mIU/mL (<0.5)
CYFRA	32.7	ng/mL (<3.5)
CEA	411	ng/mL (<5.0)
AFP	2.8	ng/mL
PSA	1.05	ng/mL
ProGRP	32.5	pg/mL
SLX	67.6	ng/mL (<38)
DUPAN-2	246	U/mL (<150)
SPan-1	5925	U/mL (<30)
CA19-9	40161	U/mL (<37)

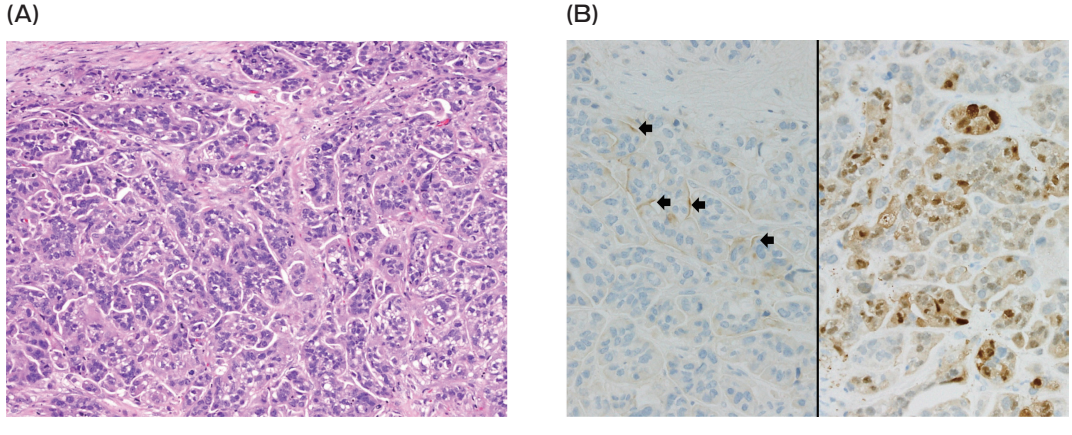

Fig. 2 Histological findings of the inguinal lymph node biopsy specimen **A**, A proliferation of atypical epithelial cells showing an invasive micro-papillary pattern was detected. Hematoxylin and eosin (H&E) staining; **B**, Uroplakin III (*left*) staining was positive with membranous staining pattern in atypical epithelial cells. IHC staining, S100-P (*right*) staining was positive in atypical epithelial cells. IHC staining.

80% dose), expecting further efficacy for the residual lesions. After 10 cycles of treatment, the patient's CA19-9, SPan-1, and CEA levels decreased to normal levels, the systemic lymph node metastases were reduced to almost the normal size, and he achieved a complete metabolic response (CMR) on FDG-PET/CT (Fig. 4). He has been well without disease progression for over 4 years.

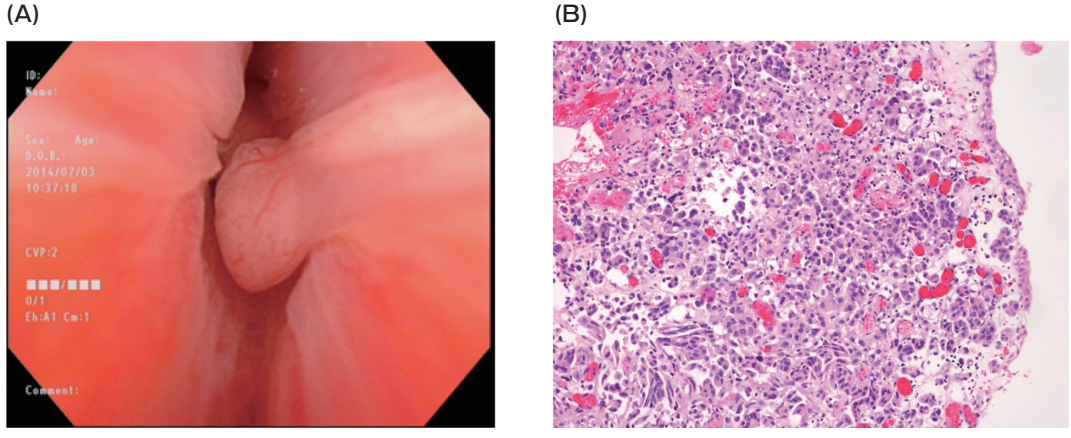

Fig. 3 Cytoscopic and histological findings of the bladder tumor. A, A pedunculated papillary tumor was observed in the prostatic urethra; B, The proliferation of atypical epithelial cells showing an invasive micro-papillary pattern was detected. H&E staining.

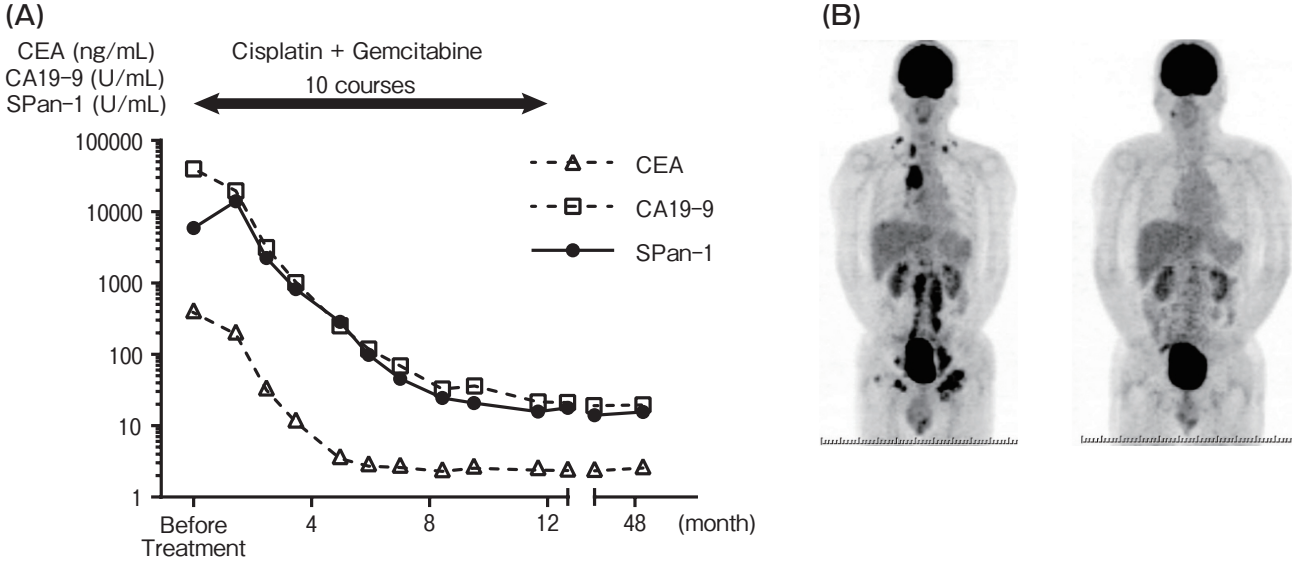

Fig. 4 A, The clinical course after systemic chemotherapy treatment; B, The multiple fluorodeoxyglucose accumulations observed by PET/CT before systemic chemotherapy (*left*) disappeared after 10 cycles of treatment (*right*).

All procedures performed in this case were in accordance with ethical standards of the institution and with the Helsinki Declaration and its amendments.

Discussion and Conclusions

Our patient's case revealed 3 significant clinical issues. First, urothelial carcinoma can present as multiple lymphadenopathy without macrohematuria. Second, Span-1 may be a helpful tumor marker for urothelial carcinoma. Third, some metastatic invasive urothelial carcinoma patients with poor prognostic factors (*e.g.*, elevation of CA19-9 and positive staining for uroplakin III) can have long survival after systemic chemotherapy comprising cisplatin and gemcitabine, by monitoring tumor markers and using FDG-PET.

Our patient presented with multiple lymphadenopathy without macrohematuria, and with elevated levels of CA19-9 and SPan-1 accompanied by life-threatening DIC and a pulmonary embolism. In general, the most common symptom of bladder cancer is painless hematuria, which occurs in approximately 85% of patients

[1], and if enough urine samples are tested, >90% of patients with cystoscopically detectable bladder cancer have at least microhematuria [2,3]. CA19-9, a carbohydrate antigen related to the Lewis A blood group antigen, is a well-known marker for pancreatic and colorectal carcinoma and is being investigated for other malignancies including bladder carcinoma [4]. Pall *et al.* reported that the sensitivity of CA19-9 was 29.3% when the reference value 37 U/mL was taken as the cut-off value of serum CA 19-9, and serum CA19-9 was significantly elevated in invasive urothelial carcinoma compared to superficial urothelial carcinoma (47.17±34.43 vs. 16.53±20.13 U/mL, $p<0.001$) [5].

SPan-1 is another carbohydrate antigen related to the Lewis A blood group antigen. Both the CA19-9 and SPan-1 assay systems recognize sialyl-lacto-N-fucopentaose II to detect malignancies [6]. Compared to CA19-9, SPan-1 is more advantageous in diagnosing pancreatic cancer patients with a Lewis-negative phenotype [7,8]. There are no published studies exploring the relationship between SPan-1 and urothelial carcinoma. In our patient's case, the urine examination showed no evidence of hematuria, and the serum examination showed an extreme elevation of CA19-9, with a SPan-1 level over 5,000 U/mL, thus representing a rare clinical case. Hydronephrosis sometimes induces the elevation of CA19-9 and Span-1 [9]. In our patient's case however, hydronephrosis was not observed at the timing of diagnosis. Moreover, his serum CA19-9 and Span-1 levels markedly decreased as the tumor regressed. Collectively, these results show that both CA19-9 and Span-1 were effective tumor markers in this case. Further reports are needed to elucidate the relationship between the elevation of SPan-1 and the prognosis or pathophysiology of urothelial carcinoma.

FDG-PET/CT is not widely used to detect and locally stage bladder cancer. This is because the physiological activity of ^{18}F-FDG, which is excreted through the urinary system, interferes with the visualization of the primary bladder cancer and locoregional lymph nodes [10]. Uroplakins, which are transmembrane proteins constituting the asymmetrical unit membrane of urothelial umbrella cells, are useful markers of carcinoma metastases of uncertain origin [11]. In our patient's case, uroplakin III staining was positive, which was the key clue to the need for further examination of the urinary system, while FDG-PET could not detect the tumor's primary site.

Elevated CA19-9 and positive staining for uroplakin III are related to metastatic urothelial carcinoma, which has a poor prognosis [5,11]. A long-term follow-up of urothelial carcinoma patients after systemic chemotherapy comprising cisplatin and gemcitabine revealed a 48-month progression-free survival rate of 9.8% [12,13]. In recent years, several research groups have reported that FDG-PET/CT can be used successfully for the early assessment of the patient's treatment response and the prognostication of bladder cancer [14,15]. Giannatempo *et al.* demonstrated that, compared to early CT, a response after 2 cycles of first-line chemotherapy detected by FDG-PET/CT was associated with longer progression-free survival and overall survival in 31 patients with advanced urothelial carcinoma [14]. Mertens *et al.* reported that the presence of extravesical FDG-avid lesions on PET/CT was an independent indicator of mortality in 211 patients with muscle-invasive bladder carcinoma [15]. Although our patient showed significant elevations of CA19-9 and SPan-1, his multiple lymph node metastases were greatly reduced after 10 cycles of chemotherapy, with a decrease of these markers to normal levels and the achievement of CMR shown by FDG-PET/CT. Together, these resulted in long survival with no recurrence. These findings may indicate that good responders who achieve a CMR on FDG-PET/CT can survive longer, even with advanced urothelial carcinoma.

In conclusion, urothelial carcinoma can present as swelling of multiple lymph nodes without hematuria, and the present case demonstrates that uroplakin III was useful for an accurate diagnosis. Some urothelial carcinomas without hematuria might be diagnosed as carcinoma of unknown origin, and thus there may be more cases of systemic invasive urothelial carcinoma than are currently recognized. The immunohistochemical staining of markers including uroplakin III should be used in cases of highly elevated CA19-9 or SPan-1 without evidence of pancreatic or colorectal cancer.

Further reports of similar cases are needed to determine the prognostic factors for long survival after systemic chemotherapy.

References

1. Kirkali Z, Chan T, Manoharan M, Algaba F, Busch C, Cheng L, Kiemeney L, Kriegmair M, Montironi R, Murphy WM, Sesterhenn IA, Tachibana M and Weider J: Bladder cancer: epidemiology, staging

and grading, and diagnosis. Urology (2005) 66: 4–34.
2. Messing EM and Vaillancourt A: Hematuria screening for bladder cancer. J Occup Med (1990) 32: 838–845.
3. Ramirez D, Gupta A, Canter D, Harrow B, Dobbs RW, Kucherov V, Mueller E, Streeper N, Uhlman MA, Svatek RS, Messing EM and Lotan Y: Microscopic haematuria at time of diagnosis is associated with lower disease stage in patients with newly diagnosed bladder cancer. BJU Int (2016) 117: 783–786.
4. Yamamoto H, Ueda Y, Maruyama T, Kondou N, Nojima M, Takiuchi H, Mori Y, Shima H and Kubota A: [A case of CA19-9 producing transitional cell carcinoma of the ureter]. Hinyokika Kiyo (2003) 49: 543–545 (in Japanese).
5. Pall M, Iqbal J, Singh SK and Rana SV: CA 19-9 as a serum marker in urothelial carcinoma. Urology Annals (2012) 4: 98–101.
6. Kawa S, Tokoo M, Oguchi H, Furuta S, Homma T, Hasegawa Y, Ogata H and Sakata K: Epitope analysis of SPan-1 and DUPAN-2 using synthesized glycoconjugates sialyllact-N-fucopentaose II and sialyllact-N-tetraose. Pancreas (1994) 9: 692–697.
7. Tsutsumi K, Kawamoto H, Hirao K, Sakakihara I, Yamamoto N, Noma Y, Fujii M, Kato H, Ogawa T, Ishida E, Kuwaki K, Nouso K, Okada H and Yamamoto K: Monitoring of CA19-9 and SPan-1 can facilitate the earlier confirmation of progressing pancreatic cancer during chemotherapy. Pancreatology (2012) 12: 409–416.
8. Ho JJ, Chung YS, Fujimoto Y, Bi N, Ryan W, Yuan SZ, Byrd JC and Kim YS: Mucin-like antigens in a human pancreatic cancer cell line identified by murine monoclonal antibodies SPan-1 and YPan-1. Cancer Res (1988) 48: 3924–3931.
9. Takase K, Inayama Y, Misaki H, Kitamura H, Nakatani Y and Hosaka M: Hydronephrosis and hydroureter with extremely high levels of serum carbohydrate antigens 19-9 and SPan-1: a case report. J Urol (1996) 155: 1386.
10. Kitajima K, Yamamoto S, Fukushima K, Minamimoto R, Kamai T and Jadvar H: Update on advances in molecular PET in urological oncology. Jpn J Urol (2016) 34: 470–485.
11. Moll R, Wu XR, Lin JH and Sun TT: Uroplakins, specific membrane proteins of urothelial umbrella cells, as histological markers of metastatic transitional cell carcinomas. Am J Pathol (1995) 147: 1383–1397.
12. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, Bodrogi I, Albers P, Knuth A, Lippert CM, Kerbrat P, Sanchez Rovira P, Wersall P, Cleall SP, Roychowdhury DF, Tomlin I, Visseren-Grul CM and Conte PF: Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol (2000) 18: 3068–3077.
13. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, Moore MJ, Zimmermann A and Arning M: Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol (2005) 23: 4602–4608.
14. Giannatempo P, Alessi A, Miceli R, Raggi D, Fare E, Nicolai N, Serafini G, Padovano B, Piva L, Biasoni D, Torelli T, Catanzaro M, Stagni S, Maffezzini M, Mariani L, Gianni AM, Sonpavde G, Salvioni R, Necchi A and Crippa F: Interim fluorine-18 fluorodeoxyglucose positron emission tomography for early metabolic assessment of therapeutic response to chemotherapy for metastatic transitional cell carcinoma. Clin Genitourin Cancer (2014) 12: 433–439.
15. Mertens LS, Fioole-Bruining A, Vegt E, Vogel WV, van Rhijn BW and Horenblas S: Impact of (18) F-fluorodeoxyglucose (FDG)-positron-emission tomography/computed tomography (PET/CT) on management of patients with carcinoma invading bladder muscle. BJU Int (2013) 112: 729–734.