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Original Article

The role of insulin-like growth factor axis in bladder cancer: a systemic review and meta analysis

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Abstract: Background: The role of the IGF axis in bladder cancer has been extensively studied in recent years, but the results are controversial. Methods: Pubmed, Embase, China national knowledge infrastructure and Wanfang databases were searched to identify eligible studies to evaluate the association among IGF-1, IGFBP-3, IGF-1R and IMP-3 expression and bladder cancer risk, depth of invasion and recurrence. Results: 15 studies were involved in the analysis, 5 of them reported the relation between serum concentration of IGF-1 or IGFBP-3 and bladder cancer risk. The difference in serum IGF-1 concentration was not significant between patients with bladder cancer and health controls (P=0.57). The serum IGFBP-3 concentration was lower in patients with bladder cancer (SMD: -0.78, 95% CI: -1.40, -0.15). 10 studies were involved in the analysis of the relation between IGF-1R or IMP-3 expression and bladder cancer. The expressions of IGF-1R and IMP-3 were elevated in MIBC compared with NMIBC (OR: 0.30, 95% CI: 0.19, 0.48 and OR: 0.30, 95% CI: 0.19, 0.46). The expressions of IGF-1R and IMP-3 were also found to be elevated in recurrent bladder cancer compared with primary bladder cancer (OR: 5.05, 95% CI: 2.43, 10.51 and OR: 2.47, 95% CI 1.48, 4.13). Conclusion: The IGF axis plays an important role in tumor proliferation and invasion, recurrence and metastasis. IGFBP-3 may be a potential serum biomarker for the screening of bladder cancer. The elevated expressions of IGF-1R and IMP3 in tissue are symbols of a highly malignant bladder cancer, and they could be utilized in the molecular classification of bladder. IGF-1R may be a promising therapeutic target for bladder cancer, but further studies are needed to evaluate the sensitivity of bladder cancer to the new targeted drugs and the predictive effect of serum IGFs in the targeted therapy.

Keywords: Bladder cancer, invasion, recurrence, IGF-1, IGFBP-3, IMP-3

Introduction

Bladder cancer is the most common urinary tract cancer and the ninth common cancer worldwide [1]. The TNM stage system is currently the most effective risk stratifying system. However, its utilization in the assessment of the malignancy and prognosis is limited due to the heterogeneity of bladder cancer. Patients with Ta-1 bladder cancer were mostly treated with bladder preservation approach because it is theoretically likely to be cured by transurethral resection of bladder tumor (TURBT). However, according to the result of a meta analysis of 19 trials and 3088 patients, 21% of the patients with NMIBC showed progression to MIBC after TURBT [2]. In patients with T2-4 bladder cancer (known as muscle-invasive bladder cancer), although radical cystectomy was performed routinely, cancer relapsed in about 50% of them and finally leads to cancer related death [3]. A better stratifying system is required to distinguish the bladder cancer with highly progressive and recurrent capacity from the low risk ones.

Recently, a large number of studies have reported possible biomarkers for the screening of potential patients and prediction of disease progression in patients with bladder cancer. Insulin-like growth factor (IGF) axis was an extensively studied system and several proteins in this axis were reported to be promising biomarkers for cancers. In our previous proteomic study, abnormally altered expressions of IGF related biomarkers were also identified in patients with bladder cancer. Thus we performed this study to verify the role of IGFs and IGF relat-

Table 1. Quality of the included studies

Study	Level of evidence	Study design	NOS score
Shariat 2003	2b	CS	7
Zhao 2003	3b	NCR	7
Zheng 2012	3b	NCR	7
Li 2007	3b	NCR	7
Mahmoud 2009	3b	NCR	7
Liu 2011	3b	NCR	8
Szarvas 2011	2b	CS	8
Xylinas 2013	2b	CS	8
Özdemir 2011	3b	NCR	5
Sitnikova 2008	2b	CS	8
Xu 2005	3b	NCR	7
Xie 2004	3b	CS	7
Rochester 2007	3b	NCR	8
Liu 2003	3b	NCR	7
Chen 2010	3b	NCR	7
Safarinejad 2011	3b	NCR	8

CS: consecutive observational study; NCR: nonconsecutive retrospective study; NOS: Newcastle-Ottawa Scale for observational studies.

ed proteins as potential biomarkers for bladder cancer.

Materials and methods

Literature search and study selection

A comprehensive literature search was performed in March 2013 using Pubmed, Embase, China national knowledge infrastructure and Wanfang databases to identify possible data resources. The reference list of included studies and related reviews were also examined to identify articles not captured by the primary search.

Studies published before May 2014 discussing expression of IGF-1, IGF-1R, IGFBP-3 and IMP-3 in bladder cancer were examined. Studies reporting on circulating concentration or expression of these proteins in tissue in patients with bladder cancer were included for further screening. This process was completed by two independent reviewers. Disagreements were resolved through discussion.

Eligible studies had to fulfill the following criteria: 1) Testing of IGF-1, IGF-1R, IGFBP-3 or IMP-3 in serum or tumor tissue of bladder cancer patients. 2) All patients diagnosed with bladder cancer were confirmed by histopathological examinations. 3) Studies reported sufficient data to calculate the mean with standard deviation (SD) or odds ratio (OR) with 95% confidence interval (CI).

Articles were excluded for the following reasons: 1) Reviews and case reports. 2) Studies without valid data or with improper data. 3) Duplicated reports.

Study quality assessment

The level of evidence was evaluated according to the criteria of Oxford Center for Evidence-Based Medicine. The methodological quality of each study was assessed with the Newcastle-Ottawa Scale (NOS).

Data extraction

Two reviewers examined the full texts of the included studies separately. For the included studies, data on characteristics of the tumor, expression of IGF-1, IGF-1R, IGFBPs and IMP3 in blood or bladder tissue, and data on survival were extracted.

Statistical analysis

The serum concentrations of IGF-1 and IGFBP-3 were assessed by mean and standard deviation (SD). For the studies reporting on serum concentrations of IGF-1 and IGFBP-3 in mean and range, the SMD were calculated with the method described by Hozo et al. [4]. Meta analyses were carried out using the "metan" command of STATA 12.0 (Stata Corporation, Collage Station, Texas, USA). The relation between depth of tumor invasion, recurrence and expression of IGF-1R and IMP-3 in cancer tissue was evaluated by OR and 95% CI. I-squared test was used to evaluate the heterogeneity among studies. If the heterogeneity was not significant, pooled estimates would be calculated with the fixed-effect model (Mantel-Haenszel method [5]); otherwise the random-effect model (DerSimonian-Laird method [6]) would be used.

The pooled effect was determined by Z test. The result was considered statistically significant when $P < 0.05$. Leave-one-out sensitivity analysis was performed to access the impact of the individual data set to the pooled results [7].

Results

After removing duplicates, a total of 2880 articles (109 in English, 2761 in Chinese) were

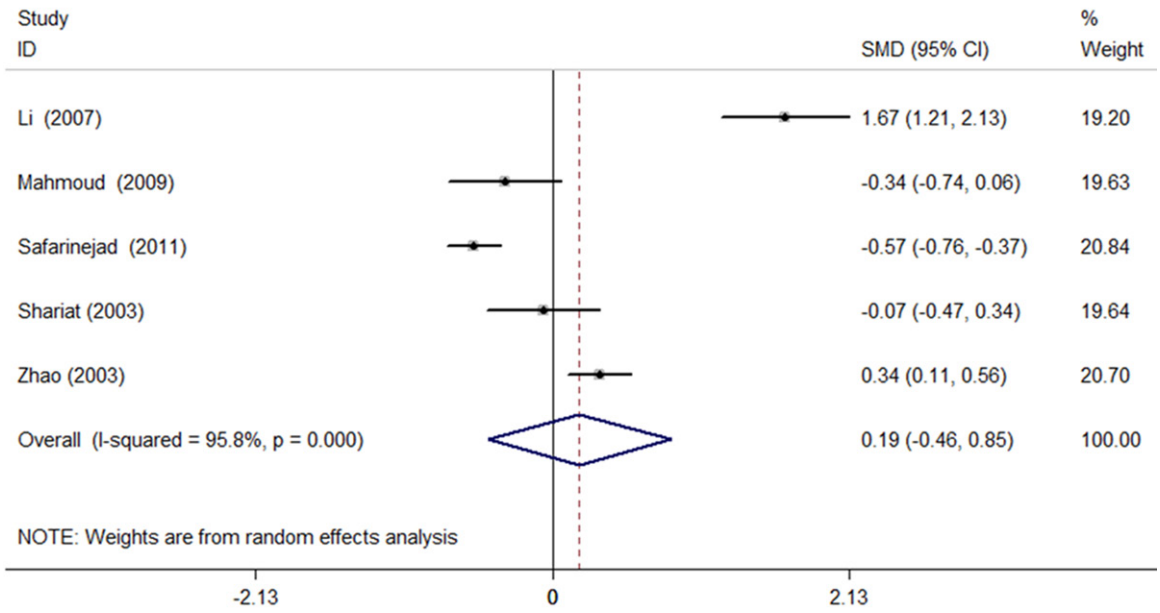

Figure 1. Forest plot of concentrations of IGF-1 in bladder cancer versus healthy control.

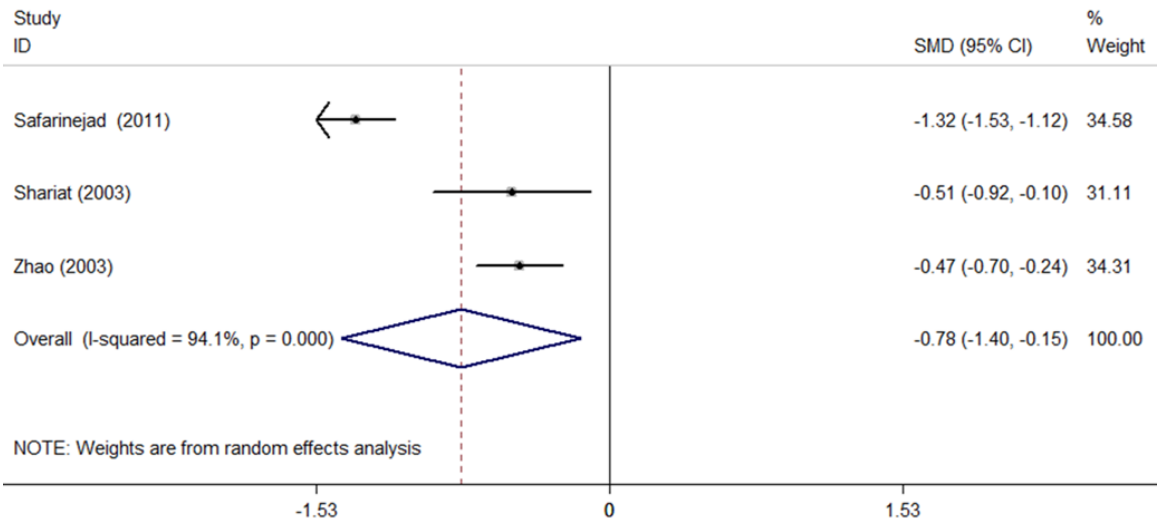

Figure 2. Forest plot of concentrations of IGFBP-3 in bladder cancer versus healthy control.

examined. 2831 articles were excluded by review of titles and abstracts. The full texts of the remaining 49 articles were examined. 6 studies reported on serum concentration of IGF-1 and IGFBP3. 5 studies were included for the analysis of IGF1R, and 5 studies for the analysis of IMP3. The quality of the included studies was showed in **Table 1**.

Five studies reported the serum concentration of IGF-1 and IGFBP3 in patients with bladder cancer and healthy controls [8-12]. The I^2 values of the two datasets are 95.8% and 94.1%, respectively, so the random effect model was used. The pooled mean difference for IGF-1 was -0.95, 95% CI (-45.82, 27.72) (*P*=0.63) (**Figure 1**). The pooled mean difference for IGFBP-3 was -0.6, 95% CI (-11.1, -0.09) (*P*=0.02) (**Figure 2**).

A total of 5 studies (one in English, and four in Chinese), including 349 patients with bladder cancer and 54 controls, reported expression of IGF1R in tissue [13, 14]. The expression of IGF1R in tissue was found to be significantly associated with bladder cancer (I^2=0, fixed

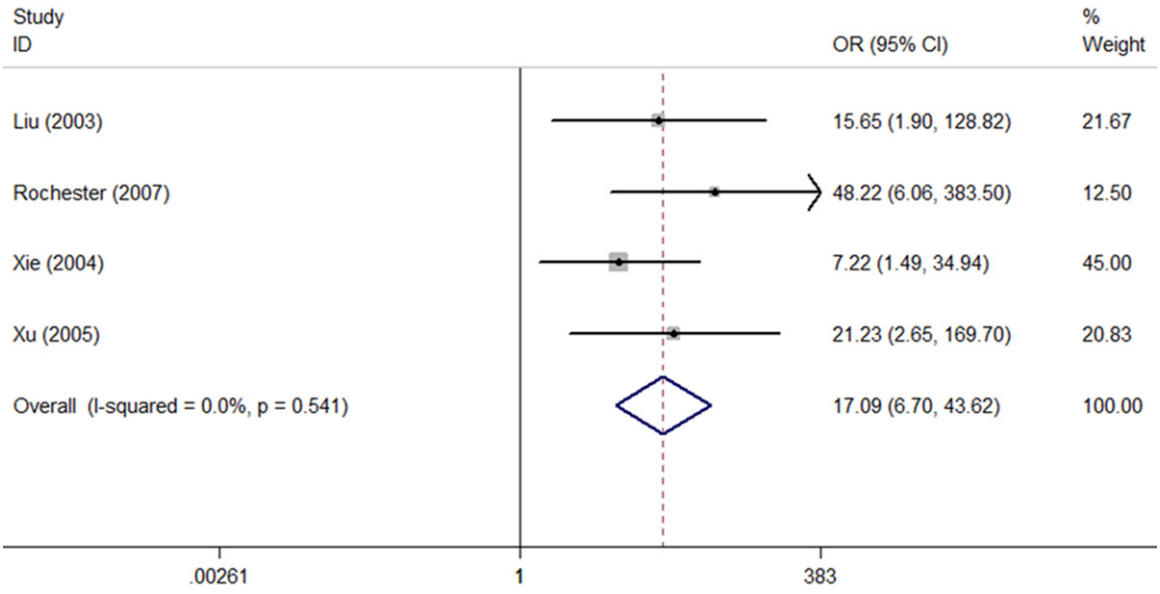

Figure 3. Forest plot of expression of IGF-1R in bladder cancer versus normal urothelial tissue.

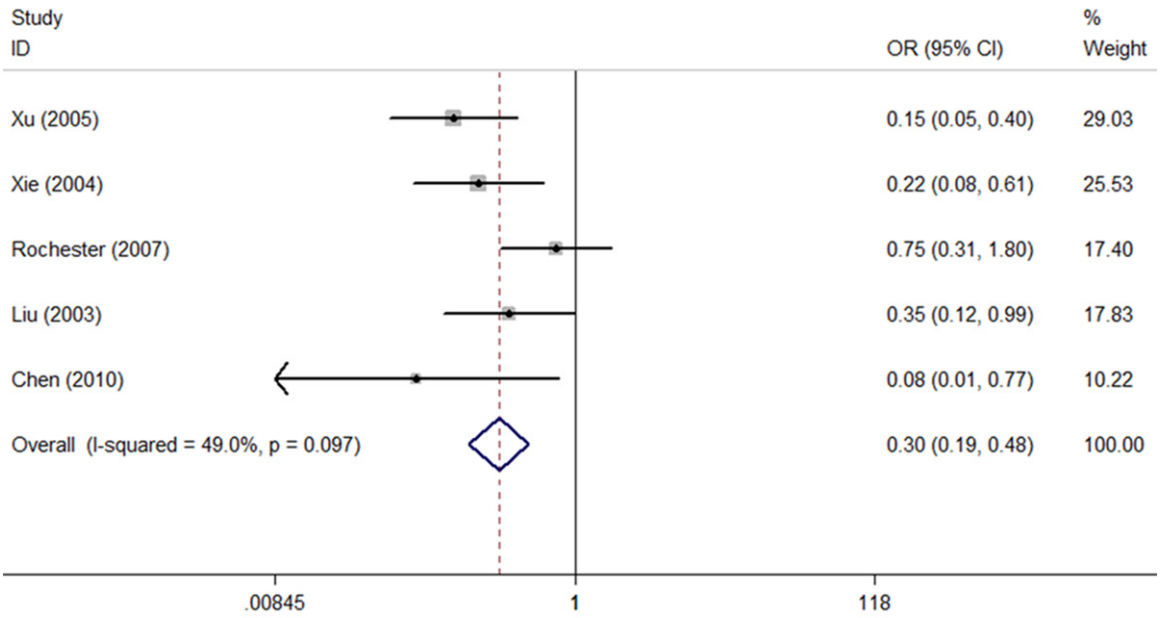

Figure 4. Forest plot of expression of IGF-1R in non-muscle invasive bladder cancer versus muscle invasive bladder cancer.

effect, OR=17.09 95% CI [6.70, 43.62], **Figure 3**). For depth of invasion, the I^2 value of the dataset is 49% (*P*=0.541), therefore fixed effect model was used. The pooled odd was lower in NMIBC group (fixed effect, OR=0.30 95% CI [0.19, 0.48]) (**Figure 4**). The major heterogeneity comes from the study of Rochester et al. In this study, the expression of IGF-1R was detected by immunochemical staining of whole-mount sections in 55 samples and tissue microarrays (TMA) in the other 80 samples [13]. The IGF-1R positive ratio of cases examined by TMAs is higher than whole-mount sections. When the cases examined by TMA were removed, the pooled OR was 0.23 (95% CI: 0.14, 0.40, I^2=0, fixed effect). With regards to recurrence, the expression of IGF1R was found to be strongly associated with bladder cancer recurrence.

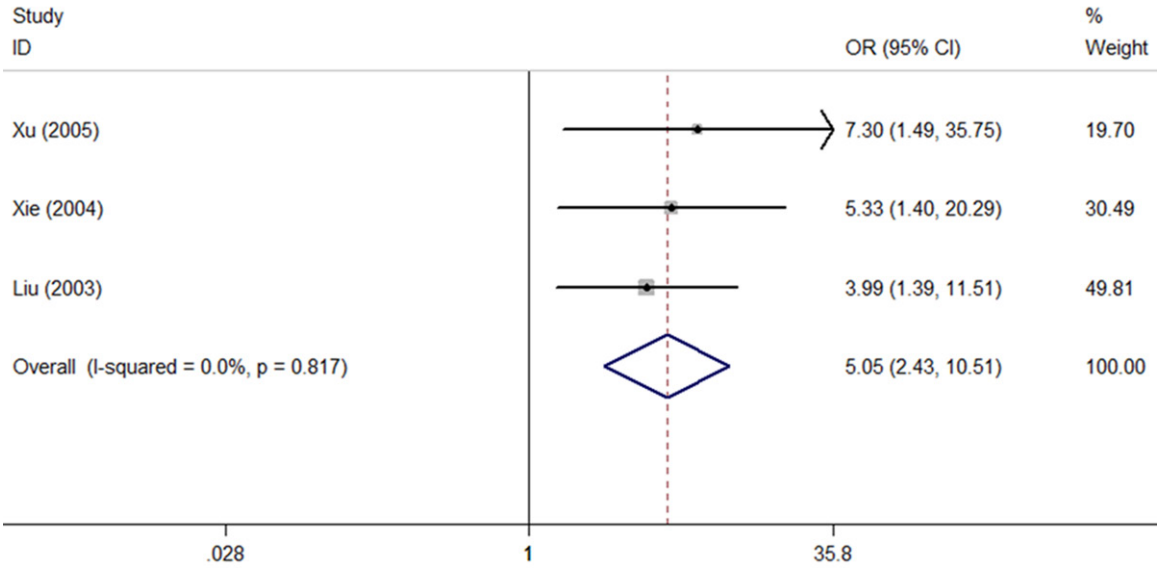

Figure 5. Forest plot of expression of IGF-1R in recurrent bladder cancer versus primary bladder cancer.

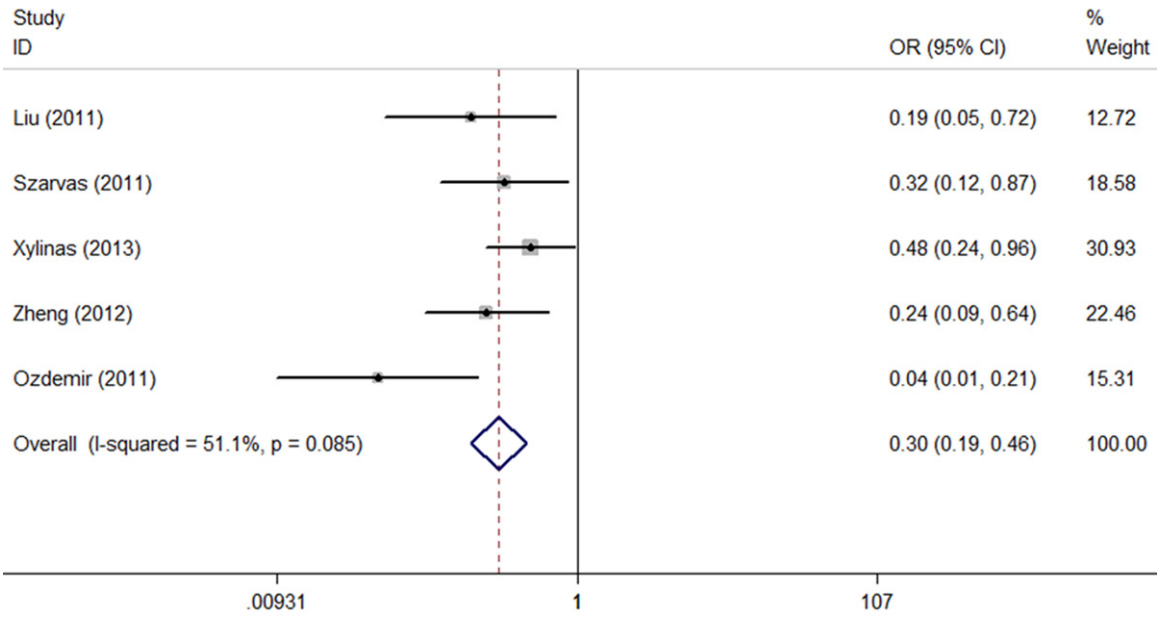

Figure 6. Forest plot of expression of IMP-3 in non-muscle invasive bladder cancer versus muscle invasive bladder cancer.

(I^2=0%, fixed effect, OR=5.05 95% CI [2.43, 10.51]) (**Figure 5**).

With respect to the expression of IMP3 in tissue, 5 studies, a total of 214 patients with NMIBC and 483 patients with MIBC were included [15-18]. With regards to depth of invasion, the pooled odd was lower in NMIBC group versus MIBC group (I^2=51.1%, fixed effect, NMIBC vs. MIBC: OR=0.3095% CI [0.19, 0.46]) (**Figure 6**), and was lower in T1 group compared with T2 group (I^2=26%, fixed effect, T1 vs. T2: OR=0.39 [0.21. 073]) (**Figure 7**). The major heterogeneity comes from the study of Özdemir et al. It can be explained by the selection bias of this study, because only patients with T0-2 bladder cancer were involved. After removal of this study, the pooled OR is 0.36 (95% CI: 0.23, 0.57). With regards to recurrence, the pooled odd was larger in recurrent bladder cancer

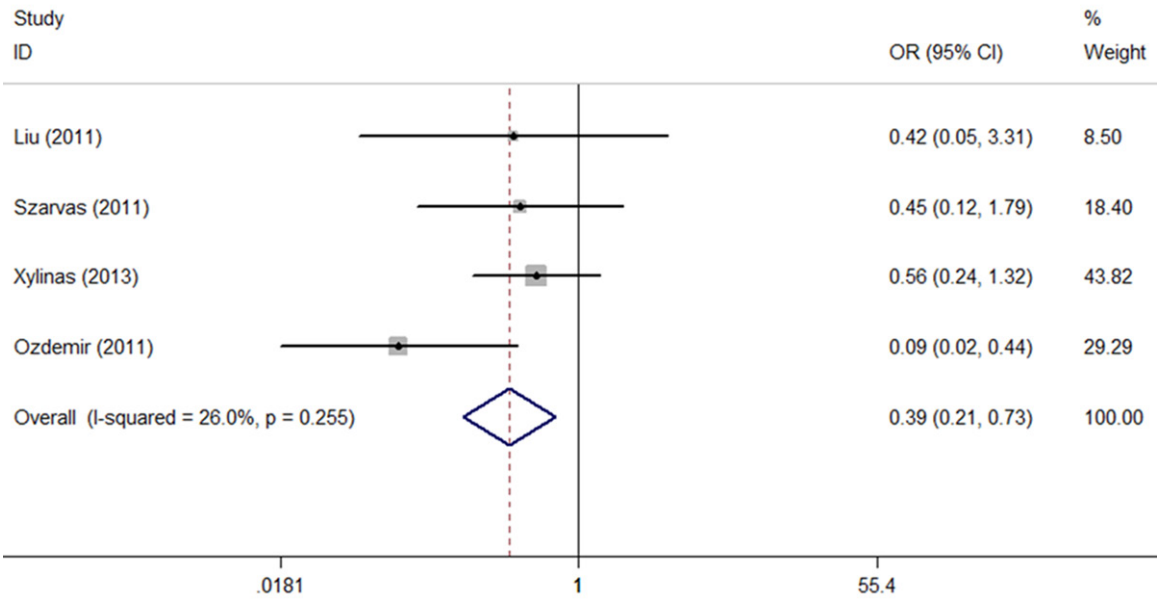

Figure 7. Forest plot of expression of IMP-3 in T1 bladder cancer versus T2 bladder cancer.

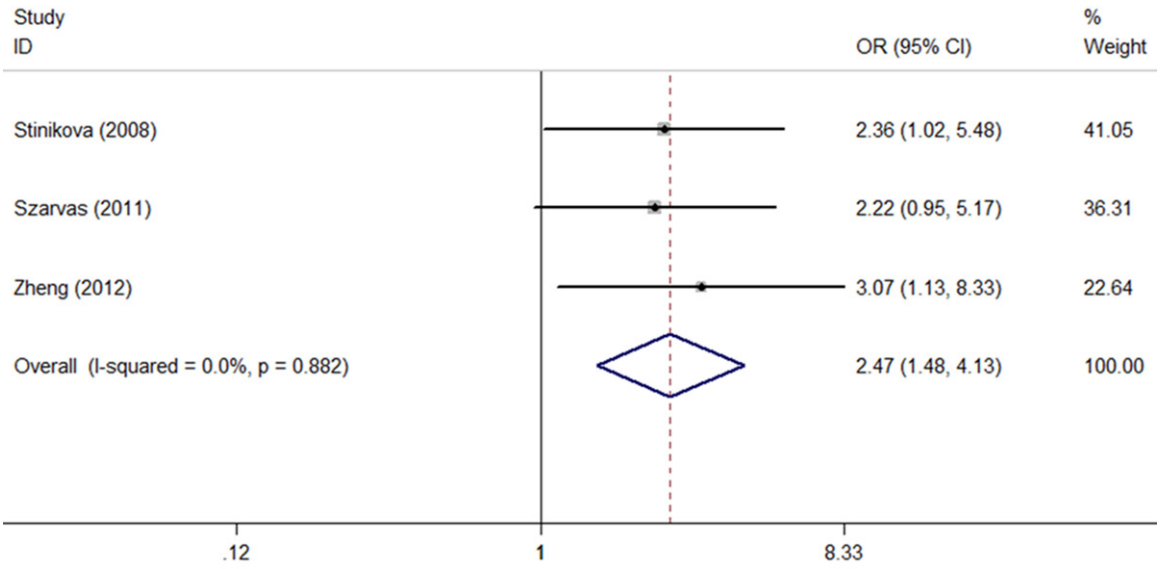

Figure 8. Forest plot of expression of IMP-3 in recurrent bladder cancer versus primary bladder cancer.

(recurrent vs. primary bladder cancer: I^2=0, fixed effect, OR=2.47 [1.48, 4.13]) (**Figure 8**). 3 studies reported the relation between IMP3 expression and survival (**Table 2**).

Discussion

IGFs are multi-functional peptides that regulate cell proliferation, differentiation and apoptosis. Serum concentrations of IGF-1 and IGFBP-3 were reported to be associated with several life style carcinogenic factors and environmental toxicities [19]. The altered IGF axis may play a key role in the carcinogenesis.

In many cancers, such as prostate, breast, colon, and lung cancer, altered serum concentrations of IGF-1 and IGFBP-3 have been reported [20]. However, reports on concentrations of serum IGF-1 in patients with bladder cancer came to conflicted outcomes. In a case-control study of 154 patients with bladder cancer and 154 health controls reported by Zhao et al. [9], concentrations of serum IGF-1 elevated signifi-

Table 2. Studies reporting on association between IMP-3 expression and survival

Study	Stage	Region	Median follow-up	No. of patients	Treatment	Survival
Sitnikova 2008	Ta-1	USA	35 months	214	TURB with/without BCG	DFS: 2.8 (1.2-6.7) PFS: 6.5 (2.2-19.0)
Szarvas 2012	Ta-4	Germany	20 months	90	RC in 75 patients PC/TURB in 15 patients	DSS: 2.2 (1.2-4.1) MFS: 2.1 (0.7-5.9)
Xylinas 2013	Ta-4	Not reported	128 months	384	RC	DSS1.4 (1.0-1.8) RFS: 1.7 (1.3-2.3)

DFS: disease-free survival; PFS: progression-free survival; DSS: disease-specific survival; MFS: metastasis-free survival; RFS: recurrence-free survival; TURB: transurethral resection of bladder tumor; RC: radical cystectomy; PC: partial cystectomy.

cantly in patients with bladder cancer, however, in the study of Safarinejad et al. [11], concentrations of serum IGF-1 were lower in patients with bladder cancer than health controls. In the studies of Shariat et al. and Mahmoud et al. [8, 10], the difference of serum IGF-1 between patients and controls was not statistically significant. Our result of the meta analysis suggests that the serum IGF-1 is not statistically different between the bladder cancer patients and health people and therefore not an eligible biomarker for bladder cancer.

IGFBP-3 is an important regulator of IGFs. Approximately 75 percent of serum IGFs are bound to IGFBP-3 [21]. IGFBP-3 can inhibit cell proliferation and enhance cell apoptosis by attenuating the effect of IGFs or directly binding with the IGFBP-3 receptor [22]. The pooled serum concentration of IGFBP-3 was lower in patients with bladder cancer compared with healthy controls, and a lower serum level of IGFBP-3 was reported to be associated with lymph node metastasis and poor clinical outcome after radical cystectomy when adjusted for IGF-I level [8]. It may be a potential serum biomarker for bladder cancer, but further studies are needed to evaluate its efficiency.

Free of lamina muscularis infiltration can be either the symbol of bladder cancer with low malignancy or a temporal status of highly invasive bladder cancer. Better risk stratification system is desperately needed for the assessment of heterogeneity of NMIBC behavior. Several biomarkers have been studied for their potential application in the assessment of tumor invasiveness, metastasis and recurrence. However, their predictive effect is far from satisfying.

Type I insulin-like growth factor receptor (IGF-1R) is a transmembrane protein tyrosine kinase which mediates the biological effects of IGF-1 and most of the actions of IGF-2 [23]. Its expression in normal tissue is low, but high in bladder cancer (OR=17.09 95% CI [6.70 43.62]). More importantly, our finding demonstrated that the expression of IGF-1R is significantly related to the depth of invasion (OR: 0.31 95% CI [0.19, 0.49]) and bladder cancer recurrence (OR: 5.05 95% CI [2.43, 10.51]). In a retrospective study, IGF-1R overexpression was associated with overall mortality and cancer-specific mortality [24]. Therefore the IGF-1R status could be included in the risk stratification system of bladder cancer.

Insulin-like growth factor II mRNA-binding protein 3 (IMP-3) is a member of the IMP family, which plays an important role in RNA trafficking and stabilization, cell growth, and cell migration during the early stages of embryogenesis [25]. It was rarely detected in adult normal tissues but over-expression of IMP-3 was reported in urothelial tumors [26]. IMP-3 plays a critical role in regulation of cell proliferation via an IGF-2-dependent pathway. We investigated the expression of IMP-3 in NMIBC and MIBC. The result showed that IMP3 status were significantly related to the depth of invasion (NMIBC vs. MIBC: OR 0.34 95% CI [0.21, 0.54]; T1 vs. T2: OR 0.31 [0.17, 0.57]). Relation between IMP-3 and tumor progression was also proved in a cohort, in which the patients with IMP-3 positive NMIBC were found more likely to develop a MIBC (OR: 6.5 95% CI [2.2, 19.0]) [27]. These findings suggest that IMP-3 is a potential biomarker for the evaluation of tumor invasiveness and prediction of progression. Correlation of IMP-3 and tumor recurrence were also studied, remarkable correlation was found between the IMP-3 status and recurrence (recurrent bladder cancer vs. primary bladder cancer: OR 2.47 95% CI [1.48, 4.13]). Moreover, the IMP-3 status was significantly related to disease-spe-

cific survival and recurrence-free survival in three cohorts [15, 16, 27]. The IMP-3 status should be utilized in the assessment of invasion, recurrence, and metastasis risk of bladder cancer, especially NMIBC.

As IGF-1R and IMP-3 are rarely expressed in normal tissue, but up-regulated in cancer tissue, they may be ideal therapeutic targets. Compared with the traditional chemotherapy regimens, treatments targeting IGF axis may destroy cancer cells with better specificity and it may show better efficiency in preventing tumor progression and recurrence. Since its expression is higher in muscle invasive and recurrent bladder cancer, it may be more effective on high risk NMIBC and MIBC, and could be a reasonable option for the salvage treatment after bladder cancer recurrence.

Several IGF-1R monoclonal antibodies, such as AVE1642, AMG479, R1507 and Figitumumab, have been developed. The IGF-1R targeted drugs achieved well tolerance and durable response in several kinds of cancers [28-31]. In a recent phase I study, 48 patients with advanced solid tumors received AVE1642 (three weekly, dosed at 6 mg/kg), combined with docetaxel, gemcitabine and erlotinib, or doxorubicin. The treatment was well tolerated and durable disease control were achieved in 44% patients [28]. With respect to biomarkers for IGF targeted therapy sensitivity, the serum concentration of free or total IGF-1 or IGF-2 appear to correlate with response to IGF-1R targeted therapy [28, 32]. However, numbers of cases in these studies were small and no study has specifically studied the application of these drugs in bladder cancer. Further researches are needed to evaluate the effect of these targeted drugs and the relation between expressions of IGF related biomarkers and sensitivity to IGF1R-targeted therapy in bladder cancer.

In conclusion, IGF axis plays an important role in tumor proliferation and invasion, recurrence and metastasis. IGFBP-3 may be a potential serum biomarker for the screening of bladder cancer. The elevated expression of IGF-1R and IMP3 in tissue is a symbol of a highly malignant bladder cancer, and could be utilized in the molecular classification of bladder. Since IGF-1R is rarely expressed in normal urothelial tissue but over-expressed in bladder cancer, it may be a promising therapeutic target for bladder cancer, but further studies are needed to evaluate the sensitivity of bladder cancer to the new targeted drugs and predictive effect of serum IGFs in the targeted therapy.

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Disclosure of conflict of interest

None.

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References

[1] Siegel R, Naishadham D and Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11-30.

[2] van den Bosch S and Alfred Witjes J. Long-term cancer-specific survival in patients with high-risk, non-muscle-invasive bladder cancer and tumour progression: a systematic review. Eur Urol 2011; 60: 493-500.

[3] Stein JP and Skinner DG. Radical cystectomy for invasive bladder cancer: long-term results of a standard procedure. World J Urol 2006; 24: 296-304.

[4] Hozo SP, Djulbegovic B and Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5: 13.

[5] Mantel N and Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-748.

[6] DerSimonian R and Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.

[7] Patsopoulos NA, Evangelou E and Ioannidis JP. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. Int J Epidemiol 2008; 37: 1148-1157.

[8] Shariat SF, Kim J, Nguyen C, Wheeler TM, Lerner SP and Slawin KM. Correlation of preoperative levels of IGF-I and IGFBP-3 with pathologic parameters and clinical outcome in patients with bladder cancer. Urology 2003; 61: 359-364.

[9] Zhao H, Grossman HB, Spitz MR, Lerner SP, Zhang K and Wu X. Plasma levels of insulin-like growth factor-1 and binding protein-3, and

their association with bladder cancer risk. J Urol 2003; 169: 714-717.
[10] Mahmoud MA, Ali MH, Hassoba HM and Elhadidy GS. Serum interleukin-8 and insulin like growth factor-1 in Egyptian bladder cancer patients. Cancer Biomark 2010; 6: 105-110.
[11] Safarinejad MR, Shafiei N and Safarinejad SH. The association between bladder cancer and a single nucleotide polymorphism (rs2854744) in the insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3) gene. Arch Toxicol 2011; 85: 1209-1218.
[12] H H, Yun L, F YY and S YC. Clinical signifcance of serum IGF-I and VEGF level in bladder tumor. International Journal of Urology 2010; 17: 29-29.
[13] Rochester MA, Patel N, Turney BW, Davies DR, Roberts IS, Crew J, Protheroe A and Macaulay VM. The type 1 insulin-like growth factor receptor is over-expressed in bladder cancer. BJU Int 2007; 100: 1396-1401.
[14] Xie QX, Lin XC, Zhang MF, Han CX and Guo YH. Expression of IGF-I and IGF-IR in bladder cancer. Ai Zheng 2004; 23: 707-709.
[15] Szarvas T, vom Dorp F, Niedworok C, Melchior-Becker A, Fischer JW, Singer BB, Reis H, Bankfalvi A, Schmid KW, Romics I, Ergun S and Rubben H. High insulin-like growth factor mRNA-binding protein 3 (IMP3) protein expression is associated with poor survival in muscle-invasive bladder cancer. BJU Int 2012; 110: E308-317.
[16] Xylinas E, Cha EK, Khani F, Kluth LA, Rieken M, Volkmer BG, Hautmann R, Kufer R, Chen YT, Zerbib M, Rubin MA, Scherr DS, Shariat SF and Robinson BD. Association of oncofetal protein expression with clinical outcomes in patients with urothelial carcinoma of the bladder. J Urol 2014; 191: 830-841.
[17] Ozdemir NO, Turk NS and Duzcan E. IMP3 expression in urothelial carcinomas of the urinary bladder. Turk Patoloji Derg 2011; 27: 31-37.
[18] Zheng JB, Li JH, Jiang HF, Yang GL, Zhang LH and Bo JJ. The expression of IMP3 in bladder cancer and its association with clinical pathological Characteristics. J Chin Physician 2012; 14: 533-535.
[19] Kaklamani VG, Linos A, Kaklamani E, Markaki I and Mantzoros C. Age, sex, and smoking are predictors of circulating insulin-like growth factor 1 and insulin-like growth factor-binding protein 3. J Clin Oncol 1999; 17: 813-817.
[20] Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM and Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 2004; 363: 1346-1353.
[21] Jones JI and Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. Endocr Rev 1995; 16: 3-34.
[22] Nickerson T, Huynh H and Pollak M. Insulin-like growth factor binding protein-3 induces apoptosis in MCF7 breast cancer cells. Biochem Biophys Res Commun 1997; 237: 690-693.
[23] Blakesley VA, Stannard BS, Kalebic T, Helman LJ and LeRoith D. Role of the IGF-I receptor in mutagenesis and tumor promotion. J Endocrinol 1997; 152: 339-344.
[24] Gonzalez-Roibon N, Kim JJ, Faraj SF, Chaux A, Bezerra SM, Munari E, Ellis C, Sharma R, Keizman D, Bivalacqua TJ, Schoenberg M, Eisenberger M, Carducci M and Netto GJ. Insulin-like Growth Factor-1 Receptor Overexpression Is Associated With Outcome in Invasive Urothelial Carcinoma of Urinary Bladder: A Retrospective Study of Patients Treated Using Radical Cystectomy. Urology 2014; 83: 1444.e1-6.
[25] Mueller-Pillasch F, Pohl B, Wilda M, Lacher U, Beil M, Wallrapp C, Hameister H, Knochel W, Adler G and Gress TM. Expression of the highly conserved RNA binding protein KOC in embryogenesis. Mech Dev 1999; 88: 95-99.
[26] Li L, Xu H, Spaulding BO, Cheng L, Simon R, Yao JL, di Sant'Agnese PA, Bourne PA and Huang J. Expression of RNA-binding protein IMP3 (KOC) in benign urothelium and urothelial tumors. Hum Pathol 2008; 39: 1205-1211.
[27] Sitnikova L, Mendese G, Liu Q, Woda BA, Lu D, Dresser K, Mohanty S, Rock KL and Jiang Z. IMP3 predicts aggressive superficial urothelial carcinoma of the bladder. Clin Cancer Res 2008; 14: 1701-1706.
[28] Macaulay VM, Middleton MR, Protheroe AS, Tolcher A, Dieras V, Sessa C, Bahleda R, Blay JY, LoRusso P, Mery-Mignard D and Soria JC. Phase I study of humanized monoclonal antibody AVE1642 directed against the type 1 insulin-like growth factor receptor (IGF-1R), administered in combination with anticancer therapies to patients with advanced solid tumors. Ann Oncol 2013; 24: 784-791.
[29] Molife LR, Fong PC, Paccagnella L, Reid AH, Shaw HM, Vidal L, Arkenau HT, Karavasilis V, Yap TA, Olmos D, Spicer J, Postel-Vinay S, Yin D, Lipton A, Demers L, Leitzel K, Gualberto A and de Bono JS. The insulin-like growth factor-I receptor inhibitor figitumumab (CP-751,871) in combination with docetaxel in patients with advanced solid tumours: results of a phase Ib dose-escalation, open-label study. Br J Cancer 2010; 103: 332-339.
[30] Tolcher AW, Sarantopoulos J, Patnaik A, Papadopoulos K, Lin CC, Rodon J, Murphy B, Roth B, McCaffery I, Gorski KS, Kaiser B, Zhu M, Deng H, Friberg G and Puzanov I. Phase I, pharmaco-

kinetic, and pharmacodynamic study of AMG 479, a fully human monoclonal antibody to insulin-like growth factor receptor 1. J Clin Oncol 2009; 27: 5800-5807.

[31] Mahadevan D, Sutton GR, Arteta-Bulos R, Bowden CJ, Miller PJ, Swart RE, Walker MS, Haluska P, Munster PN, Marshall J, Hamid O and Kurzrock R. Phase 1b study of safety, tolerability and efficacy of R1507, a monoclonal antibody to IGF-1R in combination with multiple standard oncology regimens in patients with advanced solid malignancies. Cancer Chemother Pharmacol 2014; 73: 467-473.

[32] Juergens H, Daw NC, Geoerger B, Ferrari S, Villarroel M, Aerts I, Whelan J, Dirksen U, Hixon ML, Yin D, Wang T, Green S, Paccagnella L and Gualberto A. Preliminary efficacy of the anti-insulin-like growth factor type 1 receptor antibody figitumumab in patients with refractory Ewing sarcoma. J Clin Oncol 2011; 29: 4534-4540.